=> fil reg
FILE 'REGISTRY' ENTERED AT 08:50:05 ON 07 NOV 2001
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

STRUCTURE FILE UPDATES: 5 NOV 2001 HIGHEST RN 367247-87-8
DICTIONARY FILE UPDATES: 5 NOV 2001 HIGHEST RN 367247-87-8

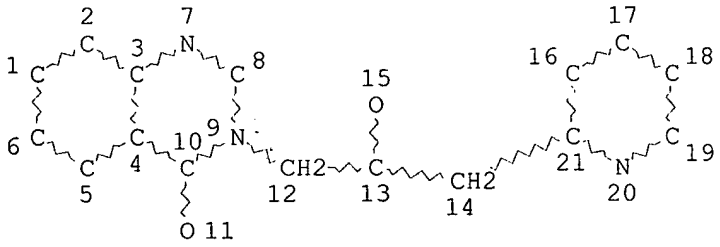
TSCA INFORMATION NOW CURRENT THROUGH July 7, 2001

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER see HELP CROSSOVER for details.

Calculated physical property data is now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> d sta que l20
L1 STR

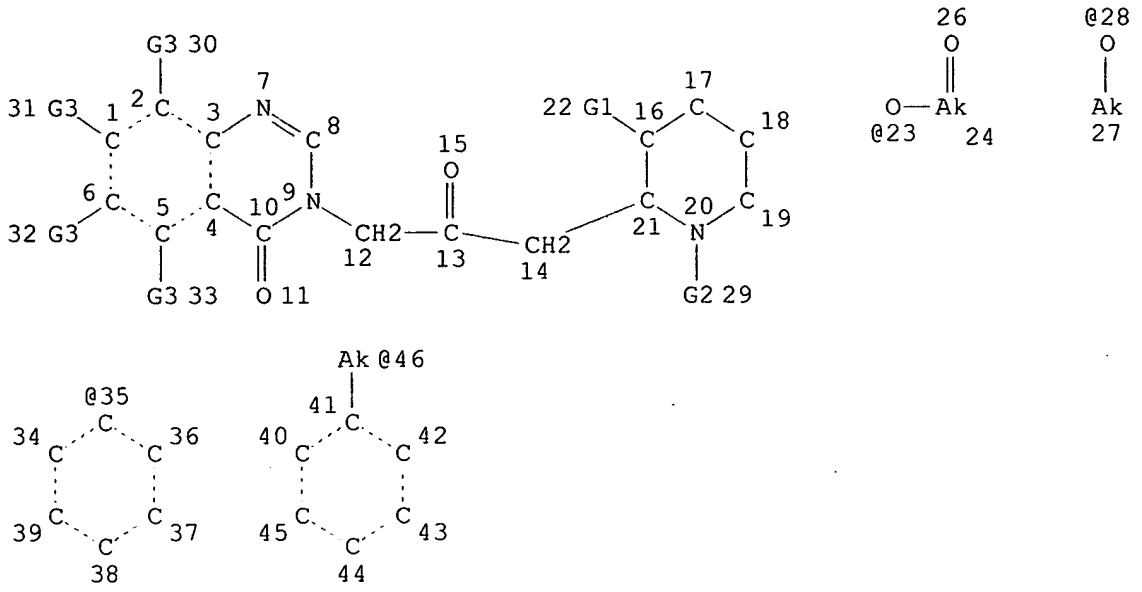


NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 21

STEREO ATTRIBUTES: NONE

L3	273	SEA	FILE=REGISTRY	SSS FUL	L1
L4	1	SEA	FILE=REGISTRY	ABB=ON PLU=ON	HALOFUGINONE/CN
L5	27	SEA	FILE=REGISTRY	ABB=ON PLU=ON	L3 AND C16H17BRCLN3O3
L6	18	SEA	FILE=REGISTRY	ABB=ON PLU=ON	55837-20-2/CRN
L7	18	SEA	FILE=REGISTRY	ABB=ON PLU=ON	L5 AND L6
L8	9	SEA	FILE=REGISTRY	ABB=ON PLU=ON	L5 NOT L7
L9	4	SEA	FILE=REGISTRY	ABB=ON PLU=ON	L8 NOT 7 BROMO 6 CHLORO
L10	5	SEA	FILE=REGISTRY	ABB=ON PLU=ON	L8 NOT L9
L11	23	SEA	FILE=REGISTRY	ABB=ON PLU=ON	(L4 OR L6 OR L7 OR L10)
L12		STR			



VAR G1=OH/23/28
VAR G2=H/28
VAR G3=H/X/NO2/35/46/AK/28
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 45

STEREO ATTRIBUTES: NONE

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L15          81 SEA FILE=REGISTRY SUB=L3 CSS FUL L12
L16          58 SEA FILE=REGISTRY ABB=ON  PLU=ON  L15 NOT (L10 OR L11)
L17          57 SEA FILE=REGISTRY ABB=ON  PLU=ON  L16 NOT C16H16CL3N3O3
L18           1 SEA FILE=REGISTRY ABB=ON  PLU=ON  L16 NOT L17
L19          80 SEA FILE=REGISTRY ABB=ON  PLU=ON  L15 NOT L18
L20          80 SEA FILE=REGISTRY ABB=ON  PLU=ON  (L9 OR L11 OR L19)


=> d his

     (FILE 'HOME' ENTERED AT 07:46:41 ON 07 NOV 2001)
               SET COST OFF

     FILE 'REGISTRY' ENTERED AT 07:46:49 ON 07 NOV 2001
L1               STR
L2            11 S L1
L3           273 S L1 FUL
                 SAV L3 KWON762/A
                 E HALOFUGINONE/CN
L4             1 S E3
L5            27 S L3 AND C16H17BRCLN3O3
                 SEL RN L4
L6            18 S E1/CRN
L7            18 S L5 AND L6
L8             9 S L5 NOT L7
L9             4 S L8 NOT 7 BROMO 6 CHLORO
L10            5 S L8 NOT L9
L11           23 S L4,L6,L7,L10
L12              STR L1
L13            2 S L12 SAM SUB=L3
```

```
L14           2 S L12 CSS SAM SUB=L3
L15          81 S L12 CSS FUL SUB=L3
                SAV L15 KWON762A/A
L16          58 S L15 NOT L10,L11
L17          57 S L16 NOT C16H16CL3N3O3
L18           1 S L16 NOT L17
L19          80 S L15 NOT L18
L20          80 S L9,L11,L19
L21         193 S L3 NOT L20
L22         179 S L21 AND (NC5 AND NCNC3-C6)/ES
L23          14 S L21 NOT L22

     FILE 'HCAPLUS' ENTERED AT 07:59:36 ON 07 NOV 2001
L24         226 S L20
L25         182 S HALOFUGINON?
L26         238 S L24,L25
                E PINES M/AU
L27         114 S E3,E4,E5
                E VLODAVSKY I/AU
L28         216 S E3-E5
                E VLODAVSK I/AU
L29          10 S E5,E6
                E NAGLER A/AU
L30         120 S E3,E4,E13,E14
                E HAZUM E/AU
L31         111 S E3,E4
L32          31 S L26 AND L27-L31
L33           9 S L32 AND EXTRACELLULAR?(L)MATRI?
L34         197 S L26 AND (PD<=19980813 OR PRD<=19980813 OR AD<=19980813)
L35          22 S L32 AND L34
L36           6 S L33 AND L35
L37          22 S L35,L36
L38           9 S L32 NOT L37
L39         209 S L26 AND (PD<=19990813 OR PRD<=19990813 OR AD<=19990813)
L40         205 S L26 AND  PY<=1999
L41         209 S L34,L39,L40
L42          26 S L32 AND L41
L43           5 S L32 NOT L42
                E COLLAGEN/CW
L44          22 S E3,E4,E7 AND L41
                E COLLAGEN/CT
                E E3+ALL
                E E2+ALL
L45       57946 S E5,E4+NT
L46      211933 S E56+NT
                E E57+ALL
L47        9447 S E14,E13+NT
L48       23650 S EXTRACELLULAR?(L)MATRI?
L49           6 S CKROX
                E TRANSCRIPTION FACTOR/CT
                E E63+ALL
L50       74892 S E4,E3+NT
                E E124+ALL
L51       57986 S E4,E3+NT
                E E24+ALL
L52        1373 S E4,E3+NT
                E E10+ALL
L53       57986 S E4,E3+NT
L54         187 S HSP47 OR HSP 47
L55       15100 S HEAT(L)SHOCK(L)PROTEIN
                E HEAT SHOCK PROTEIN/CT
                E HEAT-SHOCK/CT
                E E19+ALL
L56       10421 S E4-E7,E3+NT
                E CYTOKINE/CW
L57       76150 S E3,E4,E6
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                E CYTOKINE/CT
                E E6+ALL
L58        17576 S E13,E14,E12+NT
                E E45+ALL
L59       136052 S E5,E4+NT
L60        23881 S IL1B OR (IL OR INTERLEUKIN)(L)(1B OR 1(L)BETA)
L61        35295 S TNFA OR ATNF OR (TNF OR TUMOR(L)NECROSIS(L)FACTOR)(L)ALPHA
L62          123 S  TUMOUR(L)NECROSIS(L)FACTOR(L)ALPHA
L63        10897 S NFKB OR NF(L)(KB OR KAPPA(L)B)
L64         7246 S NUCLEAR FACTOR (L)(KB OR KAPPA(L)B)
L65         1053 S COLLAGENASE(L)TYPE () (4 OR IV)

     FILE 'REGISTRY' ENTERED AT 08:24:25 ON 07 NOV 2001
L66            1 S 9040-48-6
                E TUMOR NECROSIS FACTOR/CN
L67            1 S E3
                E TUMOR NECROSIS FACTOR-.ALPHA./CN
                E TUMOR NECROSIS FACTOR .ALPHA./CN
L68            1 S E3

     FILE 'HCAPLUS' ENTERED AT 08:25:24 ON 07 NOV 2001
L69          920 S L66,L67,L68
L70           25 S L41 AND L45-L65,L69
L71            5 S GENE/CW AND L41
L72            5 S GENES/CW AND L41
L73            3 S GENETIC/CW AND L41
L74           25 S L70-L73
L75          150 S (1 OR 63 OR 15 OR 26)/SC,SX AND L41
L76           22 S L75 AND L74
L77            3 S L74 NOT L76
L78           29 S L41 AND TISSUE
L79            1 S L41 AND ?TRAUM?
                E ANIMAL TISSUE/CT
                E E3+ALL
L80            9 S L41 AND E3,E2+NT
L81            8 S L80 NOT 17/SC
L82           20 S L78 NOT L80
L83            9 S L82 NOT 17/SC,SX
L84            6 S L83 AND (1 OR 63)/SC,SX NOT CHICKEN
L85            4 S L84 NOT (QUAIL OR RATS)/TI
                E WOUND/CW
L86         9823 S E3,E5
                E WOUND/CT
                E E3+ALL
L87         2469 S E4,E3+NT
                E E8+ALL
L88         5920 S E3,E2+NT
                E E12+ALL
L89         1809 S E3+NT
                E E7+ALL
                E E10+ALL
L90         5809 S E3,E4,E2+NT
                E E11+ALL
                E E9+ALL
L91          681 S E4+NT
L92       211933 S E3+NT
L93           11 S L41 AND L86-L92
L94            9 S L93 NOT CHICKEN
                E FIBROSIS/CW
L95         6711 S E3
                E FIBROSIS/CT
                E E3+ALL
L96         5481 S E2+NT
L97       169659 S ?FIBRO?
                E LIVER FIBROSIS/CT
                E E3+ALL
```

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                E LIVER FIBROSIS/CT
                E E3+ALL
L98          170 S E1
L99          817 S E2
                E CIRRHOSIS/CW
L100        7041 S E3
                E CIRRHOSIS/CT
                E E3+ALL
L101        6898 S E5,E6,E4+NT
L102       14943 S ?CIRRHO?
L103      140467 S ?INFLAM?
                E INFLAM/CW
L104       58649 S E4,E5
                E INFLAM/CT
                E E8+ALL
L105       59040 S E2+NT
L106       18414 S E57+NT OR E56+NT OR E55
                E E55+ALL
L107       42443 S E4-E7,E2,E11-E16
                E LEUKOTRIENE/CT
                E E27+ALL
L108       10758 S E12,E13,E11+NT
                E E24+ALL
L109         817 S E6,E5+NT
                E KIDNEY FIBROSIS/CT
                E RENAL FIBROSIS/CT
                E E3+ALL
L110         140 S E1
L111         298 S E2
                E PULMONARY FIBROSIS/CT
L112         316 S E3
                E E3+ALL
L113         907 S E2
                E CARDIAC FIBROSIS/CT
                E HEART FIBROSIS/CT
L114        5131 S (HEART OR CARDI? OR MYOCARD?)(L)?FIBRO?
L115         169 S NEOANGIOGEN?
                E ANGIOGEN/CW
L116        6003 S E4
L117         789 S E5
                E ANGIOGEN/CT
                E E4+ALL
L118        4883 S E5+NT
L119        1760 S E7+NT
L120         789 S E8+NT
L121      109153 S E9+NT
L122       13124 S ?ANGIOGEN?
                E ADHESION/CT
                E E4+ALL
L123        1686 S E1
                E E2+ALL
L124       19574 S E2,E1+NT
L125        7399 S ?PSORIA?
                E PSORIA/CW
L126        5126 S E5
                E PSORIA/CT
                E E6+ALL
L127        5126 S E4+NT
L128         414 S KELOID
                E KELOID/CT
                E E3+ALL
L129         314 S E4+NT
L130        4036 S SCAR OR SCARING
                E SCAR/CW
L131           3 S E3
                E SCAR/CT
```

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.                E E5+ALL
L132         216 S E4
L133          29 S L41 AND L95-L132
L134          28 S L133 NOT 17/SC,SX
L135          24 S L134 NOT CHICKEN
                 E SKIN/CT
                 E E3+ALL
L136          12 S L41 AND E4+NT
L137           0 S L41 AND (E42+NT OR E43+NT)
                 E E46+ALL
L138           5 S L41 AND (E4 OR E3+NT)
L139          36 S L42,L76,L79,L81,L85,L94,L135,L136,L138
L140          41 S L43 OR L139
L141          36 S L140 AND (1 OR 63)/SC,SX
L142           5 S L141 AND CHICKEN
L143          31 S L141 NOT L142
L144          30 S L143 NOT 17/SC
L145          30 S L144 AND L24-L65,L69-L143
                 SEL HIT RN

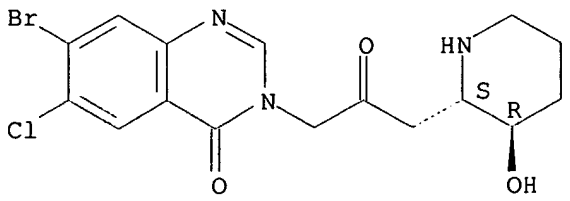
     FILE 'REGISTRY' ENTERED AT 08:49:30 ON 07 NOV 2001
L146           2 S E1-E2

     FILE 'REGISTRY' ENTERED AT 08:50:05 ON 07 NOV 2001

=> d ide can tot l146

L146 ANSWER 1 OF 2  REGISTRY  COPYRIGHT 2001 ACS
RN   55837-20-2  REGISTRY
CN   4(3H)-Quinazolinone, 7-bromo-6-chloro-3-[3-[(2R,3S)-3-hydroxy-2-
     piperidinyl]-2-oxopropyl]-, rel- (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   4(3H)-Quinazolinone, 7-bromo-6-chloro-3-[3-(3-hydroxy-2-piperidinyl)-2-
     oxopropyl]-, trans-(.+-.)-
OTHER NAMES:
CN   4(3H)-Quinazolinone, 7-bromo-6-chloro-3-[3-(3-hydroxy-2-piperidinyl)-2-
     oxopropyl]-, trans-
CN   Halofuginone
FS   STEREOSEARCH
MF   C16 H17 Br Cl N3 O3
CI   COM
LC   STN Files:   ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS,
       BIOTECHNO, CA, CABA, CAPLUS, CASREACT, CBNB, CHEMLIST, CIN, DDFU,
       DIOGENES, DRUGNL, DRUGU, DRUGUPDATES, EMBASE, IPA, MRCK*, PHAR, PROMT,
       RTECS*, TOXLIT, USAN, USPATFULL, VETU
         (*File contains numerically searchable property data)
     Other Sources:   WHO

Relative stereochemistry.
```




```
**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

             135 REFERENCES IN FILE CA (1967 TO DATE)
               3 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
             135 REFERENCES IN FILE CAPLUS (1967 TO DATE)
```

REFERENCE 1: 135:251986

REFERENCE 2: 135:164621

REFERENCE 3: 135:142301

REFERENCE 4: 135:142255

REFERENCE 5: 135:131807

REFERENCE 6: 135:24735

REFERENCE 7: 135:4660

REFERENCE 8: 134:366805

REFERENCE 9: 134:366803

REFERENCE 10: 134:366802

L146 ANSWER 2 OF 2 REGISTRY COPYRIGHT 2001 ACS
RN **9040-48-6** REGISTRY
CN Gelatinase (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Collagenase IV
CN Collagenase type IV
CN Type IV collagen metalloproteinase
CN Type IV collagenase
CN Type IV collagenase/gelatinase
MF Unspecified
CI MAN
LC STN Files: ADISNEWS, AGRICOLA, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPLUS, CHEMCATS, CIN, CSCHEM, EMBASE, PIRA, PROMT, TOXLIT, USPATFULL

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
919 REFERENCES IN FILE CA (1967 TO DATE)
11 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
920 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 135:269801

REFERENCE 2: 135:257369

REFERENCE 3: 135:240556

REFERENCE 4: 135:239527

REFERENCE 5: 135:235903

REFERENCE 6: 135:179631

REFERENCE 7: 135:151547

REFERENCE 8: 135:117219

REFERENCE 9: 135:102548

REFERENCE 10: 135:87170

=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 08:50:31 ON 07 NOV 2001
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1947 - 7 Nov 2001 VOL 135 ISS 20
FILE LAST UPDATED: 6 Nov 2001 (20011106/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

This file supports REG1stRY for direct browsing and searching of all substance data from the REGISTRY file. Enter HELP FIRST for more information.

HCAplus now provides online access to patents and literature covered in CA from 1947 to the present. On April 22, 2001, bibliographic information and abstracts were added for over 2.2 million references published in CA from 1947 to 1966.

=> d all hitstr tot l145

L145 ANSWER 1 OF 30 HCAPLUS COPYRIGHT 2001 ACS
AN 2001:703740 HCAPLUS
DN 135:251986
TI Methods for treating **fibroproliferative** diseases with antiproliferative or **antifibrotic** agents, especially antisense c-Jun oligonucleotides
IN Peterson, Theresa C.
PA Dalhousie University, Can.
SO U.S., 13 pp., Cont.-in-part of U.S. 6,025,151.
CODEN: USXXAM
DT Patent
LA English
IC ICM C12Q001-02
ICS C12Q001-00; C12Q001-50
NCL 435029000
CC **1-12** (Pharmacology)
Section cross-reference(s): 9, **63**
FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	US 6294350	B1	20010925	US 1999-433621	19991102	<--
	US 5985592	A	19991116	US 1997-870096	19970605	<--
	US 6025151	A	20000215	US 1998-92317	19980605	<--
	WO 2001032156	A2	20010510	WO 2000-IB1731	20001102	

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 1997-870096 A2 19970605 <--
US 1998-92317 A2 19980605 <--
US 1999-433621 A1 19991102

AB In accordance with the present invention, **fibroproliferative** disease or condition characterized by such symptoms as increased levels of c-Jun homodimers, increased heterodimerization of c-Jun with another signaling peptide, increased levels of phosphorylated c-Jun, or increased presence of Jun kinase are treated by administering to the subject an amt. of a compd. effective to ameliorate one or more of the symptoms of the

disease or condition, for example, an antiproliferative or **antifibrotic** agent. Preferred compds. for administration according to the invention are antisense c-Jun oligonucleotides and compds. that block c-Jun phosphorylation, such as pentoxifylline, or a functional deriv. or metabolite thereof. Also provided by the present invention are in vitro tests for identifying whether a test compd. is useful for treatment of a subject afflicted with such a disease and kits useful for conducting such assays.

ST **fibroproliferative** disease treatment antiproliferative **antifibrotic** agent; antiproliferative antisense oligonucleotide **fibroproliferative** disease cJun

IT Peptides, biological studies
RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BIOL (Biological study); PROC (Process)
(ATF2; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

IT Angiotensin receptors
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(AT1, inhibitors; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

IT **Hepatitis**
(C; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

IT **Transcription factors**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(CREB (cAMP-responsive element-binding); antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

IT Eye, disease
Graves' disease
(Graves' ophthalmopathy; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

IT Sarcoma
(Kaposi's; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

IT Neoplasm
(Li-Fraumeni syndrome; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

IT **Transcription factors**
RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence)
(**NF-.kappa.B (nuclear factor .kappa.B)**; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

IT Peptides, biological studies
RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BIOL (Biological study); PROC (Process)
(Nrf1; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

IT Eye
(Tenon's capsule, **fibroproliferation**; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

IT Leukemia

(acute myelogenous; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

IT Abdomen
(adhesions; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

IT **Fibrosis**
(**antifibrotics**; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

IT Alzheimer's disease
Animal **tissue** culture
Anti-Alzheimer's agents
Antitumor agents
Drug screening
Epithelium
Fibroblast
Hematopoietic precursor cell
Keloid
Kidney, disease
Leprosy
Mesenchyme
Multiple sclerosis
Myelodysplastic syndromes
Myeloproliferative disorders
Neoplasm
Neuroglia
Phosphorylation, biological
Picrorhiza kurroa
Signal transduction, biological
Silicosis
Silybum marianum
Test kits
(antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

IT Platelet-derived growth factors
Tumor necrosis factors
RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence)
(antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

IT Antisense oligonucleotides
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

IT Decorins
Phosphatidylcholines, biological studies
Tocopherols
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

IT Bronchi
(bronchiolitis, obliterative; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

IT Signal peptides
RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence);

BPR (Biological process); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(c-Jun heterodimerization with; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

IT **Transcription factors**
RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence); BPN (Biosynthetic preparation); BPR (Biological process); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence); PREP (Preparation); PROC (Process)
(c-jun; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

IT Malaria
(cerebral; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

IT Intestine, disease
(colitis, collagenous; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

IT **Cardiovascular** system
(disease; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

IT **Drugs**
Ergot (Claviceps)
(drug-induced ergotism; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

IT Reproductive tract
(female, cancer; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

IT Intestine
Lung
Skin
(**fibroblasts** of; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

IT Radiation
(**fibrosis** from; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

IT **Heart**, disease
Kidney, disease
Liver, disease
Lung, disease
Peritoneum
(**fibrosis**; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

IT **Gene**, animal
RL: BPN (Biosynthetic preparation); BPR (Biological process); BIOL (Biological study); PREP (Preparation); PROC (Process)
(for c-Jun; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

IT Neuroglia
(glioblastoma, sporadic; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

IT Neuroglia
(glioblastoma; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

IT Kidney, disease
(glomerulonephritis; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)
IT Neutrophil
(infiltration; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)
IT Intestine, disease
(**inflammatory**; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)
IT **Cytokines**
RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence)
(**inflammatory**; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)
IT Drug delivery systems
(inhalants; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)
IT Drug delivery systems
(injections, i.m.; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)
IT Drug delivery systems
(injections, i.v.; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)
IT Lung, disease
(interstitial; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)
IT Brain, disease
(malaria; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)
IT Antitumor agents
(mammary gland; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)
IT Kidney
(mesangium; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)
IT Leukemia
(myelogenous; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)
IT Liver
(**myofibroblasts** of; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)
IT Mammary gland
(neoplasm, inhibitors; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)
IT Mammary gland
(neoplasm; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)
IT Nerve, neoplasm
(neuroblastoma; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating

fibroproliferative diseases)

IT Drug delivery systems
(oral; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

IT Proteins, specific or class
RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence)
(p65, **NF-.kappa.B** p65; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

IT Phosphatidylcholines, biological studies
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(polyenyl-; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

IT Proliferation inhibition
(proliferation inhibitors; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

IT Disease, animal
(proliferative; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

IT Drug delivery systems
(rectal; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

IT **Connective tissue**
(scleroderma; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

IT Shock (circulatory collapse)
(septic; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

IT **Blood vessel**
(smooth muscle; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

IT **Muscle**
(smooth; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

IT Carcinoma
(squamous cell, differentiation disorder; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

IT Cell differentiation
(squamous cell, disorder; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

IT Drug delivery systems
(sustained-release; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

IT **Lupus erythematosus**
(systemic, nephritis assocd. with; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

IT Drug delivery systems
(topical; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

IT Drug delivery systems
(transdermal; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

IT **Interferons**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(.alpha.; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

IT Transforming growth factors
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(.beta.-, RII/FC; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

IT 155215-87-5, Jun kinase
RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence)
(antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

IT 217308-10-6, DNA, d(G-C-A-G-T-C-A-T-A-G-A-A-C-A-G-T-C-C-G-T-C-A-C-T-T-C-A-C-G-T)
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); PEP (Physical, engineering or chemical process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

IT 50-23-7, Hydrocortisone 54-85-3, Isoniazid 54-85-3D, Isoniazid, conjugated 59-67-6, Niacin, biological studies 64-86-8, Colchicine 107-35-7, Taurine 518-34-3, Tetrandrine 1028-33-7, Pentifylline 1405-86-3, Glycyrrhizin 6493-05-6, Pentoxifylline 6493-05-6D, Pentoxifylline, derivs. and metabolites 6493-06-7, 1H-Purine-2,6-dione, 3,7-dihydro-1-(5-hydroxyhexyl)-3,7-dimethyl- 10102-43-9, Nitric oxide, biological studies 53179-13-8, Pirfenidone 55242-55-2, Propentofylline **55837-20-2, Halofuginone** 62571-86-2, Captopril 75847-73-3, Enalapril 80288-49-9, Furafylline 83150-76-9, Octreotide 85721-33-1, Ciprofloxacin 91161-71-6, Terbinafine 114798-26-4, Losartan 119290-87-8, Acanthoic acid 120210-48-2, Tenidap
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

IT 50-88-4, Tritiated thymidine, biological studies 1148-63-6, Thymidine-.alpha.-t 42459-79-0, Uridine, 5-bromo-, labeled with tritium
RL: BPR (Biological process); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

IT 330196-64-0, Cytochrome p 450 1A2
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(inhibitors; antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

IT 9015-82-1, Angiotensin converting enzyme
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; antiproliferative or **antifibrotic** agents, esp.

antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

RE.CNT 14

RE

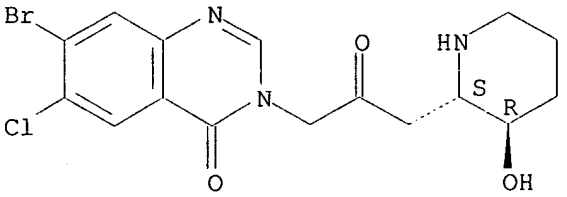
(1) Anon; DE 3604149 A1 1987 HCAPLUS
(2) Anon; WO 8700523 A2 1987 HCAPLUS
(3) Anon; WO 9219772 A1 1992 HCAPLUS
(4) Anon; EP 0544391 A1 1993 HCAPLUS
(5) Anon; WO 9502051 A2 1995 HCAPLUS
(6) Anon; WO 9526727 A1 1995 HCAPLUS
(7) Bamberger; Proc Natl Acad Sci USA 1996, V93, P6169 HCAPLUS
(8) Bessler; J Leukocyte Biol 1986, V40, P747 HCAPLUS
(9) Bianco; US 5585380 1996 HCAPLUS
(10) Bonsen; US 4265874 1981 HCAPLUS
(11) Peterson; US 5985592 1999 HCAPLUS
(12) Peterson; US 6025151 2000 HCAPLUS
(13) Theeuwes; US 4160452 1979 HCAPLUS
(14) Theeuwes; US 4256108 1981

IT **55837-20-2, Halofuginone**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiproliferative or **antifibrotic** agents, esp. antisense c-Jun oligonucleotides, for treating **fibroproliferative** diseases)

RN 55837-20-2 HCAPLUS

CN 4(3H)-Quinazolinone, 7-bromo-6-chloro-3-[3-[(2R,3S)-3-hydroxy-2-piperidinyl]-2-oxopropyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L145 ANSWER 2 OF 30 HCAPLUS COPYRIGHT 2001 ACS

AN 2001:338333 HCAPLUS

DN 134:357558

TI Methods for treating **fibroproliferative** diseases

IN Peterson, Theresa C.

PA Dalhousie University, Can.

SO PCT Int. Appl., 34 pp.
CODEN: PIXXD2

DT Patent

LA English

IC ICM A61K031-00
ICS A61K031-522; A61K045-00; A61K045-06; A61K048-00; C12Q001-48; G01N033-58; A61P019-04; A61P035-00; A61P037-00; A61P025-28; A61P043-00; A61P033-06; A61P031-12; A61P039-00; A61P035-02; A61P001-00; A61P011-00; A61P013-12; A61P009-00

CC **63-6** (Pharmaceuticals)
Section cross-reference(s): **1**, 2, 8, **15**

FAN.CNT 4

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001032156	A2	20010510	WO 2000-IB1731	20001102

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN,

YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PI US 6294350 B1 20010925 US 1999-433621 19991102 <--
PRAI US 1999-433621 A1 19991102
US 1997-870096 A2 19970605 <--
US 1998-92317 A2 19980605 <--

AB In accordance with the present invention, **fibroproliferative** disease or condition characterized by such symptoms as increased levels of c-Jun homodimers, increased heterodimerization ofc-Jun with another signaling peptide, increased levels of phosphorylated c-Jun, or increased presence of Jun kinase are treated by administering to the subject an amt. of a compd. effective to ameliorate one or more of the symptoms of the disease or condition, for example, an antiproliferative or **antifibrotic** agent. Preferred compds. for administration according to the invention are antisense c-Jun oligonucleotides and compds. that block c-Jun phosphorylation, such as pentoxifylline, or a functional deriv. or metabolite thereof. Also provided by the present invention are in vitro tests for identifying whether a test compd. is useful for treatment of a subject afflicted with such a disease and kits useful for conducting such assays.

ST antiproliferative antisense oligonucleotide **fibroproliferative** disease cJun

IT Peptides, biological studies
RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BIOL (Biological study); PROC (Process)
(ATF2; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)

IT **Hepatitis**
(C; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)

IT **Transcription factors**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(CREB (cAMP-responsive element-binding); antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)

IT Eye, disease
Graves' disease
(Graves' ophthalmopathy; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)

IT Sarcoma
(Kaposi's; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)

IT Neoplasm
(Li-Fraumeni syndrome; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)

IT **Transcription factors**
RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence)
(**NF-.kappa.B (nuclear factor .kappa.B)**; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)

IT Peptides, biological studies
RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BIOL (Biological study); PROC (Process)
(Nrf1; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)

IT Eye
(Tenon's capsule, **fibroproliferation**; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)

IT Leukemia
(acute myelogenous; antisense oligonucleotide prepns. for treating

fibroproliferative diseases)
IT Abdomen
(adhesions; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)
IT Angiotensin receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(angiotensin II AT1, inhibitors; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)
IT **Fibrosis**
(antifbrotics; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)
IT Alzheimer's disease
Animal **tissue** culture
Anti-Alzheimer's agents
Antitumor agents
Epithelium
Fibroblast
Hematopoietic precursor cell
Keloid
Kidney, disease
Leprosy
Mesenchyme
Multiple sclerosis
Myelodysplastic syndromes
Myeloproliferative disorders
Neoplasm
Neuroglia
Phosphorylation, biological
Picrorhiza kurroa
Signal transduction, biological
Silicosis
Silybum marianum
(antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)
IT Platelet-derived growth factors
Tumor necrosis factors
RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence)
(antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)
IT Antisense oligonucleotides
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)
IT Decorins
Phosphatidylcholines, biological studies
Tocopherols
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)
IT Bronchi
(bronchiolitis, obliterative; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)
IT **Transcription factors**
RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence)
(c-jun; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)
IT Malaria
(cerebral; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)

IT Intestine, disease
(colitis, collagenous; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)
IT **Cardiovascular** system
(disease; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)
IT Reproductive tract
(female, cancer; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)
IT Intestine
Lung
Skin
(**fibroblasts** of; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)
IT Radiation
(**fibrosis** from; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)
IT **Heart**, disease
Kidney, disease
Lung, disease
Peritoneum
(**fibrosis**; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)
IT Neuroglia
(glioblastoma, sporadic; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)
IT Neuroglia
(glioblastoma; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)
IT Kidney, disease
(glomerulonephritis; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)
IT Neutrophil
(infiltration; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)
IT Intestine, disease
(**inflammatory**; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)
IT **Cytokines**
RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence)
(**inflammatory**; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)
IT Drug delivery systems
(inhalants; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)
IT Cell proliferation
(inhibitors; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)
IT Drug delivery systems
(injections, i.m.; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)
IT Drug delivery systems
(injections, i.v.; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)
IT Lung, disease
(interstitial; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)
IT Brain, disease
(malaria; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)
IT Antitumor agents
(mammary gland; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)
IT Kidney

(mesangium; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)
IT Leukemia
(myelogenous; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)
IT Liver
(**myofibroblasts** of; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)
IT Mammary gland
(neoplasm, inhibitors; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)
IT Mammary gland
(neoplasm; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)
IT Nerve, neoplasm
(neuroblastoma; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)
IT Drug delivery systems
(oral; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)
IT Proteins, specific or class
RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence)
(p65; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)
IT Phosphatidylcholines, biological studies
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(polyenyl-; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)
IT Disease, animal
(proliferative; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)
IT Drug delivery systems
(rectal; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)
IT **Connective tissue**
(scleroderma; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)
IT Shock (circulatory collapse)
(septic; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)
IT **Blood vessel**
(smooth muscle; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)
IT **Muscle**
(smooth; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)
IT Carcinoma
(squamous cell, differentiation disorder; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)
IT Cell differentiation
(squamous cell, disorder; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)
IT Drug delivery systems
(sustained-release; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)
IT **Lupus erythematosus**
(systemic, nephritis; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)
IT Drug delivery systems
(topical; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)
IT Drug delivery systems
(transdermal; antisense oligonucleotide prepns. for treating

fibroproliferative diseases)

IT **Interferons**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(.alpha.; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)

IT Transforming growth factors
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(.beta.-, RII/FC; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)

IT 155215-87-5, Jun kinase
RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence)
(antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)

IT 217308-10-6
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)

IT 50-23-7, Hydrocortisone 54-85-3, Isoniazid 59-67-6, Niacin, biological studies 64-86-8, Colchicine 107-35-7, Taurine 518-34-3, Tetrandrine 1028-33-7, Pentifylline 1405-86-3, Glycyrrhizin 6493-05-6, Pentoxifylline 6493-06-7 10102-43-9, Nitric oxide, biological studies 53179-13-8, Pirfenidone 55242-55-2, Propentofylline **55837-20-2**, **Halofuginone** 62571-86-2, Captopril 75847-73-3, Enalapril 80288-49-9, Furafylline 83150-76-9, Octreotide 85721-33-1, Ciprofloxacin 91161-71-6, Terbinafine 114798-26-4, Losartan 119290-87-8, Acanthoic acid 120210-48-2, Tenidap
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)

IT 50-88-4, Tritiated thymidine, biological studies 42459-79-0
RL: BPR (Biological process); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)

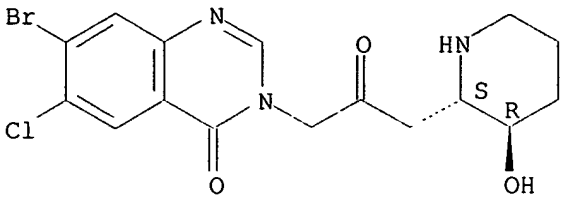
IT 330196-64-0, Cytochrome p 450 1A2
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(inhibitors; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)

IT 9015-82-1, Angiotensin converting enzyme
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)

IT **55837-20-2, Halofuginone**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antisense oligonucleotide prepns. for treating **fibroproliferative** diseases)

RN 55837-20-2 HCAPLUS
CN 4(3H)-Quinazolinone, 7-bromo-6-chloro-3-[3-[(2R,3S)-3-hydroxy-2-piperidinyl]-2-oxopropyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



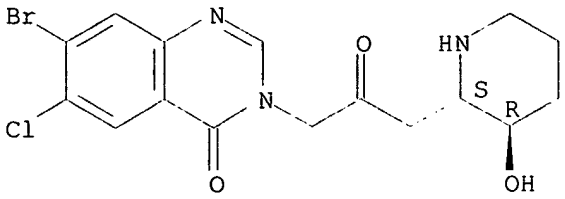
L145 ANSWER 3 OF 30 HCAPLUS COPYRIGHT 2001 ACS
AN 2001:185574 HCAPLUS
DN 134:212791
TI Promotion of wound healing with **halofuginone**
IN **Pines, Mark; Vlodavsky, Israel; Nagler, Arnon**
PA Hadasit Medical Research Services and Development Company Ltd., Israel
SO PCT Int. Appl., 38 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-505
CC **63-7** (Pharmaceuticals)
Section cross-reference(s): **1**
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001017531	A1	20010315	WO 1999-IL441	19990909
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9952995	A1	20010410	AU 1999-52995	19990909
PRAI WO 1999-IL441	A	19990909		

OS MARPAT 134:212791
AB A promotor of wound healing and an inhibitor of formation of a urethral stricture, particularly following surgical intervention or infection in the area is disclosed. Specifically, the most preferred compd. of the present invention, **halofuginone**, can be used to prevent collagen deposition from occurring within the lumen of the urethra after such trauma, thereby inhibiting urethral stricture formation. **Halofuginone**, and related compds., are also useful for the promotion of wound healing after trauma, for example after surgery. Efficacy of 1 mg **halofuginone**/mouse in the promotion of wound healing is shown.
ST wound healing promotion **halofuginone**
IT **Keloid**
Wound healing promoters
(promotion of wound healing with **halofuginone**)
IT **Collagens, biological studies**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(promotion of wound healing with **halofuginone**)
IT Urethra
(strictures of; promotion of wound healing with **halofuginone**)
IT **Collagens, biological studies**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(type III; promotion of wound healing with **halofuginone**)
IT **55837-20-2, Halofuginone**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(promotion of wound healing with **halofuginone**)

RE.CNT 1
RE
(1) Nagler; US 5891879 A 1999 HCAPLUS
IT **55837-20-2, Halofuginone**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(promotion of wound healing with **halofuginone**)
RN 55837-20-2 HCAPLUS
CN 4(3H)-Quinazolinone, 7-bromo-6-chloro-3-[3-[(2R,3S)-3-hydroxy-2-piperidinyl]-2-oxopropyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L145 ANSWER 4 OF 30 HCAPLUS COPYRIGHT 2001 ACS
AN 2001:122373 HCAPLUS
DN 135:131807
TI **Halofuginone** to prevent and treat thioacetamide-induced liver **fibrosis** in rats
AU Bruck, Rafael; Genina, Olga; Aeed, Hussein; Alexiev, Rosaly; **Nagler, Arnon**; Avni, Yona; **Pines, Mark**
CS Department of Gastroenterology, Agricultural Research Organization, Bet Dagan, 50250, Israel
SO Hepatology (Philadelphia) (2001), 33(2), 379-386
CODEN: HPTLD9; ISSN: 0270-9139
PB W. B. Saunders Co.
DT Journal
LA English
CC **1-5** (Pharmacology)
AB Hepatic **fibrosis** is assocd. with the activation of hepatic stellate cells (HSC), the major source of the **extracellular matrix** (ECM) proteins. The predominant ECM protein synthesized by the HSC is collagen type I. The authors evaluated the effect of **halofuginone** - an inhibitor of collagen synthesis - on thioacetamide (TAA)-induced liver **fibrosis** in rats. In the control rats, the HSC did not express smooth muscle actin, collagen type I gene, or tissue inhibitor of metalloproteinases-2 (TIMP-2), suggesting that they were in their quiescent state. When treated with TAA, the livers displayed large **fibrous** septa, which were populated by smooth muscle actin-pos. cells expressing high levels of the collagen .alpha.1(I) gene and contg. high levels of TIMP-2, all of which are characteristic of advanced **fibrosis**. **Halofuginone** given orally before **fibrosis** induction prevented the activation of most of the stellate cells and the remaining cells expressed low levels of collagen .alpha.1(I) gene, resulting in low levels of collagen. The level of TIMP-2 was almost the same as in the control livers. When given to rats with established **fibrosis**, **halofuginone** caused almost complete resoln. of the **fibrotic** condition. The levels of collagen, collagen .alpha.1(I) gene expression, TIMP-2 content, and smooth muscle actin-pos. cells were as in the control rats. **Halofuginone** inhibited the proliferation of other cell types of the **fibrotic** liver in vivo and inhibited collagen prodn. and collagen .alpha.1(I) gene expression in the SV40-immortalized rat HSC-T6 cells in vitro. These results suggest that **halofuginone** may become an effective and novel mode of therapy in the treatment of liver **fibrosis**.
ST **halofuginone** thioacetamide liver **fibrosis** treatment

IT **Liver, disease**
(**fibrosis; halofuginone** to prevent and treat thioacetamide-induced liver **fibrosis** in rats)
IT Cell proliferation
(**halofuginone** to prevent and treat thioacetamide-induced liver **fibrosis** in rats)
IT Liver
(stellate cell; **halofuginone** to prevent and treat thioacetamide-induced liver **fibrosis** in rats)
IT **Collagens, biological studies**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(type I; **halofuginone** to prevent and treat thioacetamide-induced liver **fibrosis** in rats)
IT 62-55-5, Thioacetamide
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(**halofuginone** to prevent and treat thioacetamide-induced liver **fibrosis** in rats)
IT **55837-20-2, Halofuginone**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**halofuginone** to prevent and treat thioacetamide-induced liver **fibrosis** in rats)
RE.CNT 59
RE
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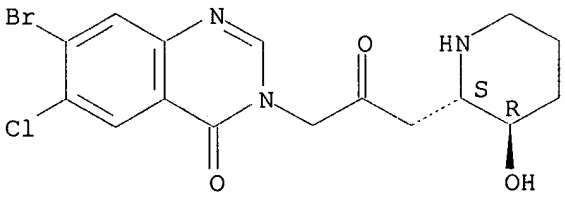
IT **55837-20-2, Halofuginone**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**halofuginone** to prevent and treat thioacetamide-induced liver **fibrosis** in rats)

RN 55837-20-2 HCAPLUS

CN 4(3H)-Quinazolinone, 7-bromo-6-chloro-3-[3-[(2R,3S)-3-hydroxy-2-piperidinyl]-2-oxopropyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L145 ANSWER 5 OF 30 HCAPLUS COPYRIGHT 2001 ACS

AN 2001:120458 HCAPLUS

DN 134:290191

TI **Halofuginone**: a potent inhibitor of critical steps in **angiogenesis** progression

AU Elkin, Michael; Miao, Hua-Quan; **Nagler, Arnon**; Aingorn, Elena; Reich, Reuven; Hemo, Itzhak; Dou, Hong-Liang; **Pines, Mark**; **Vlodavsky, Israel**

CS Department of Oncology, Hadassah-Hebrew University Hospital, Jerusalem, 91120, Israel

SO FASEB J. (2000), 14(15), 2477-2485
CODEN: FAJOEC; ISSN: 0892-6638

PB Federation of American Societies for Experimental Biology

DT Journal

LA English

CC **1-8** (Pharmacology)

AB We have previously demonstrated that **halofuginone**, a low mol. wt. quinazolinone alkaloid, is a potent inhibitor of collagen .alpha.1(I) and **matrix** metalloproteinase 2 (MMP-2) gene expression. **Halofuginone** also effectively suppresses tumor progression and metastasis in mice. These results together with the well-documented role of **extracellular matrix** (ECM) components and **matrix** degrading enzymes in formation of new blood vessels led us to investigate the effect of **halofuginone** on the **angiogenic** process. In a variety of exptl. system, representing sequential events in the **angiogenic** cascade, **halofuginone** treatment resulted in profound inhibitory effect. Among these are the abrogation of endothelial cell MMP-2 expression and

basement membrane invasion, capillary tube formation, and vascular sprouting, as well as deposition of subendothelial ECM. The most conclusive anti-**angiogenic** activity of **halofuginone** was demonstrated in vivo (mouse corneal micropocket assay) by showing a marked inhibition of basic **fibroblast** growth factor (bFGF) -induced neovascularization in response to systemic administration of **halofuginone**, either i.p. or in the diet. The ability of **halofuginone** to interfere with key events in neovascularization, together with its oral bioavailability and safe use as an anti-parasitic agent, make it a promising drug for further evaluation in the treatment of a wide range of diseases assocd. with pathol. **angiogenesis**.

ST **angiogenesis** inhibitor **halofuginone** vascular endothelium MMP2; antitumor metastasis **angiogenesis** inhibitor **halofuginone**

IT **Blood vessel**
(endothelium, proliferation; **halofuginone** is a potent inhibitor of crit. steps in **angiogenesis** progression)

IT **Angiogenesis inhibitors**
Basement membrane
(**halofuginone** is a potent inhibitor of crit. steps in **angiogenesis** progression)

IT **Angiogenesis**
(neovascularization, bFGF-induced; **halofuginone** is a potent inhibitor of crit. steps in **angiogenesis** progression)

IT **55837-20-2, Halofuginone**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**halofuginone** is a potent inhibitor of crit. steps in **angiogenesis** progression)

IT 106096-93-9, Basic **fibroblast** growth factor 146480-35-5, MMP 2
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**halofuginone** is a potent inhibitor of crit. steps in **angiogenesis** progression)

RE.CNT 44

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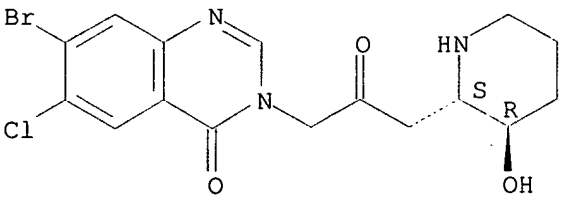
IT **55837-20-2, Halofuginone**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**halofuginone** is a potent inhibitor of crit. steps in **angiogenesis** progression)
RN 55837-20-2 HCAPLUS
CN 4(3H)-Quinazolinone, 7-bromo-6-chloro-3-[3-[(2R,3S)-3-hydroxy-2-piperidinyl]-2-oxopropyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



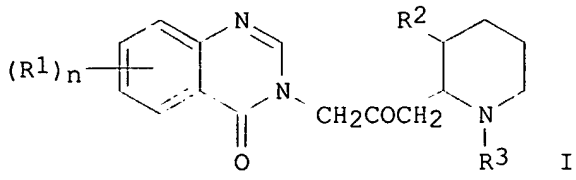
L145 ANSWER 6 OF 30 HCAPLUS COPYRIGHT 2001 ACS
AN 2000:874127 HCAPLUS
DN 134:33039
TI Intracoronary stents containing quinazolinone derivatives
IN **Nagler, Arnon; Hazum, Eli**; Geller, Ehud; Slavin, Shimon; **Vlodavsky, Israel; Pines, Mark**
PA Agricultural Research Org. Ministry of Agriculture (Gov), Israel; Hadasitmedical Research Serv. and Devel. Ltd.
SO U.S., 14 pp., Cont.-in-part of U.S. Ser. No. 180,498.
CODEN: USXXAM
DT Patent
LA English
IC A61K031-505
NCL 424423000
CC **63-7** (Pharmaceuticals)
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 6159488	A	20001212	US 1999-325198	19990603 <--
	WO 9823244	A2	19980604	WO 1997-US15254	19970814 <--

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

PRAI WO 1997-US15254 A1 19970814 <--
US 1999-180498 A2 19990329 <--

IL 1996-119162 A 19960830 <--
OS MARPAT 134:33039
GI



I

AB The invention provides an intracoronary stent coated with a quinazolinone deriv. I (n = 1,2; R1 = H, halogen, NO2, benzo, lower alkyl, Ph, and lower alkoxy; R2 = OH, OAc, lower alkoxy, and R3 = H, lower alkenoxy-carbonyl), and physiol. acceptable salts thereof, for preventing restenosis after angioplasty. A metal stent was coated with a soln. contg. polyethylene vinyl acetate and **halofuginone**, and the **halofuginone** release from the coating was detd. in vitro. Also, the antiproliferative effect of **halofuginone** on smooth muscle cells was examd.
ST coronary stent coating quinazolinone deriv; **halofuginone** coronary stent coating restenosis prevention
IT Drug delivery systems
(films; intracoronary stents coated with quinazolinone derivs. for preventing restenosis after angioplasty.)
IT Medical goods
(stents; intracoronary stents coated with quinazolinone derivs. for preventing restenosis after angioplasty.)
IT 24937-78-8, Polyethylene vinyl acetate
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(intracoronary stents coated with polymers and quinazolinone derivs. for preventing restenosis after angioplasty.)
IT **55837-20-2, Halofuginone**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(intracoronary stents coated with quinazolinone derivs. for preventing restenosis after angioplasty.)
IT 12766-00-6D, Quinazolinone, derivs.
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(intracoronary stents coated with quinazolinone derivs. for preventing restenosis after angioplasty.)
RE.CNT 13
RE
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(2) Anon; WO 9606616 1996 HCAPLUS
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(4) Granot; Biochimica et Biophysica Acta 1993, V1156, P107 HCAPLUS
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(6) Nagler; US 5891879 1999 HCAPLUS
(7) Nyska; Connective Tissue Research 1996, V34(2), P97 HCAPLUS
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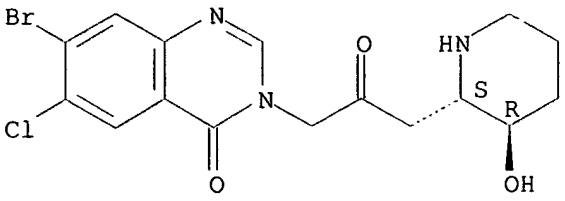
(12) Waletzky; US 3320124 1967 HCAPLUS
(13) Wiktor; US 5653727 1997
IT **55837-20-2, Halofuginone**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(intracoronary stents coated with quinazolinone derivs. for preventing restenosis after angioplasty.)
RN 55837-20-2 HCAPLUS
CN 4(3H)-Quinazolinone, 7-bromo-6-chloro-3-[3-[(2R,3S)-3-hydroxy-2-piperidinyl]-2-oxopropyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L145 ANSWER 7 OF 30 HCAPLUS COPYRIGHT 2001 ACS
AN 2000:774204 HCAPLUS
DN 134:290157
TI The effects of **halofuginone**, an inhibitor of collagen type I synthesis, on urethral stricture formation: in vivo and in vitro study in a rat model
AU **Nagler, Arnon**; Gofrit, Ofer; Ohana, Meir; Pode, Dov; Genina, Olga; **Pines, Mark**
CS Department of Bone Marrow Transplantation and Urology, Hadassah University Hospital, Jerusalem, Israel
SO J. Urol. (Baltimore) (2000), 164(5), 1776-1780
CODEN: JOURAA; ISSN: 0022-5347
PB Lippincott Williams & Wilkins
DT Journal
LA English
CC **1-8** (Pharmacology)
AB Urethral strictures are narrowing of the urethra caused by **fibrosis** due to excessive collagen prodn. in response to an insult. The effects of **halofuginone**, a potent inhibitor of collagen .alpha.1(I) gene expression, were evaluated on exptl. induced urethral strictures in vivo and on rat urethral **fibroblasts** in vitro. Applying a coagulation current to the male rat urethra produced urethral strictures. **Halofuginone** was given to the animals for 7 days, starting on the day of stricture formation, either orally at 1 and 5 ppm in the diet or by injection of 0.03% **halofuginone** soln. into the urethra. All the rats were sacrificed on day 21. The coagulation current produced reproducible strictures with a typical urethrogram appearance, which were assocd. with increases in collagen .alpha.1(I) gene expression and collagen content at the stricture site. **Halofuginone** injected into the urethra or given orally at 5 ppm normalized the urethrogram and prevented increases in collagen .alpha.1(I) gene expression and collagen content. **Halofuginone** at 10-8M inhibited the collagen secretion by **fibroblasts** derived from the rat male urethra, due to inhibition of the collagen .alpha.1(I) gene expression. Thus, **halofuginone** prevented stricture formation and may become an important mode of therapy in the prevention of restenosis during urethral stricture formation.
ST urethra stricture **halofuginone** collagen formation gene
IT Gene, animal
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(collagen .alpha.1(I); **halofuginone**, an inhibitor of collagen type I synthesis, effect on urethral stricture formation)
IT Urethra
(**halofuginone**, an inhibitor of collagen type I synthesis, effect on urethral stricture formation)
IT **Collagens, biological studies**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(type I; **halofuginone**, an inhibitor of collagen type I synthesis, effect on urethral stricture formation)
IT **55837-20-2, Halofuginone**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**halofuginone**, an inhibitor of collagen type I synthesis,

effect on urethral stricture formation)
RE.CNT 19
RE
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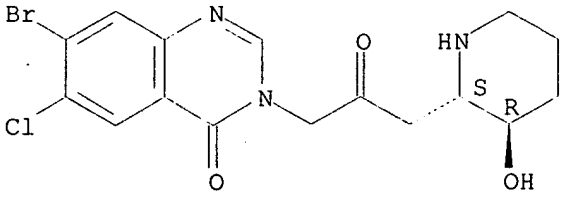
IT **55837-20-2, Halofuginone**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**halofuginone**, an inhibitor of collagen type I synthesis, effect on urethral stricture formation)
RN 55837-20-2 HCAPLUS
CN 4(3H)-Quinazolinone, 7-bromo-6-chloro-3-[3-[(2R,3S)-3-hydroxy-2-piperidinyl]-2-oxopropyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L145 ANSWER 8 OF 30 HCAPLUS COPYRIGHT 2001 ACS
AN 2000:724292 HCAPLUS
DN 134:12982
TI **Halofuginone**: from veterinary use to human therapy
AU **Pines, Mark; Vlodavsky, Israel; Nagler, Arnon**
CS Institute of Animal Science, The Volcani Center, Agricultural Research Organization, Bet Dagan, 50250, Israel
SO Drug Dev. Res. (2000), 50(3/4), 371-378
CODEN: DDREDK; ISSN: 0272-4391
PB Wiley-Liss, Inc.
DT Journal; General Review
LA English
CC **1-0** (Pharmacology)
AB A review with 57 refs. At present, **halofuginone** is the only known inhibitor of collagen synthesis that is type specific. **Halofuginone** inhibits collagen .alpha.1(I) gene expression and collagen synthesis in vitro in cell cultures and in various animal models in vivo that are characterized by excessive deposition of collagen, which results in **fibrosis**. Toxicity studies both in animals and in normal volunteers revealed no major side effects. **Halofuginone** was successfully used topically in a patient with chronic graft-vs.-host disease and at present is being tested in a clin. trial of patients with scleroderma. Collagen is an important component of the stroma and is

involved in endothelial cell migration and assembly to form and recruit new blood vessels: **angiogenesis**. Both stromal support and **angiogenesis** are crit. for tumor growth. Based on this rationale and by using various tumor models such as bladder carcinoma, prostate cancer, and glioma, it has been demonstrated that inhibition of collagen .alpha.1(I) gene expression by **halofuginone** caused inhibition of **angiogenesis**, which resulted in arrest of tumor growth. Thus, inhibition of collagen type I synthesis provides an attractive new target for cancer therapy. Many of the possible targets for **halofuginone** therapy pose enormous clin. problems, most of them currently without solns. The ability of extremely low concns. of **halofuginone**, given orally, locally or i.p., to inhibit collagen .alpha.1(I) synthesis specifically and transiently at the transcriptional level suggests that this compd. fulfills the criteria for a successful and effective **antifibrotic** and anticancer therapy.

ST review **halofuginone** pharmacol antitumor **antifibrotic** collagen formation inhibitor; **angiogenesis** inhibitor **halofuginone** review

IT **Angiogenesis inhibitors**
Antitumor agents
(**halofuginone** pharmacol., including action as)

IT **Fibrosis**
(**halofuginone** pharmacol., including **fibrosis** inhibition)

IT **Collagens, biological studies**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(type I; **halofuginone** pharmacol., including action as inhibitor of collagen type I formation)

IT **55837-20-2, Halofuginone**
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); BIOL (Biological study)
(pharmacol. of collagen synthesis inhibitor **halofuginone**)

RE.CNT 57

RE

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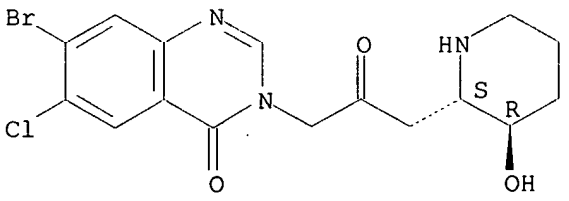
IT **55837-20-2, Halofuginone**
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); BIOL (Biological study)
(pharmacol. of collagen synthesis inhibitor **halofuginone**)
RN 55837-20-2 HCAPLUS
CN 4(3H)-Quinazolinone, 7-bromo-6-chloro-3-[3-[(2R,3S)-3-hydroxy-2-piperidinyl]-2-oxopropyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L145 ANSWER 9 OF 30 HCAPLUS COPYRIGHT 2001 ACS
AN 2000:133423 HCAPLUS
DN 132:161276
TI **Extracellular matrix**-regulating compounds, including quinazolinones, for inhibition of pathogenic processes related to **tissue trauma**
IN **Pines, Mark; Vlodavsky, Israel; Nagler, Arnon ; Hazum, Eli**
PA Hadasit Medical Research Services and Development Company Ltd., Israel; Agricultural Research Organization
SO PCT Int. Appl., 60 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K
CC **1-12** (Pharmacology)
Section cross-reference(s): **63**
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

PI WO 2000009070 A2 20000224 WO 1999-IL440 19990813 <--
WO 2000009070 A3 20001019
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
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AU 9951914 A1 20000306 AU 1999-51914 19990813 <--
EP 1109559 A2 20010627 EP 1999-936952 19990813 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO
PRAI IL 1998-125790 A 19980813 <--
US 1999-137145 P 19990601 <--
WO 1999-IL440 W 19990813 <--
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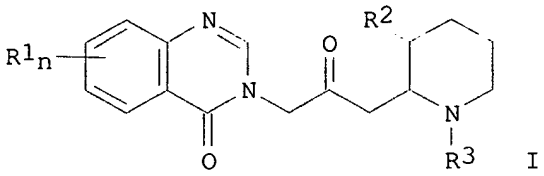


I

AB Compns. and methods are provided to prevent the pathogenic aspects of **tissue trauma** while preserving normal **tissue** repair mechanisms, based on the fact that these mols. abrogate the cascade of damage initiated by **tissue trauma**, while maintaining this the requisite healthy **extracellular matrix** economy. The compn. for regulating the **extracellular matrix** economy, comprise a pharmaceutically effective amt. of an effector in combination with a pharmaceutically acceptable carrier. Preferably, the effector is a quinazolinone deriv. More preferably, the quinazolinone deriv. is I wherein (R1 = H, halo, nitro, benzo, lower alkyl, Ph, lower alkoxy; R2 = OH, acetoxy, lower alkoxy; R3 = H, lower alkenoxy; n = 1, 2) and pharmaceutically acceptable salts thereof. Most preferably, the effector is **Halofuginone** or a pharmaceutically acceptable salt thereof.

ST quinazolinone deriv **extracellular matrix tissue trauma; Halofuginone extracellular matrix tissue trauma**

IT Proteins, specific or class
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(23-kDa highly basic protein, gene; **extracellular matrix**-regulating compds., including quinazolinones, for inhibition of pathogenic processes related to **tissue trauma**)

IT CD antigens
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(CD9, gene; **extracellular matrix**-regulating compds., including quinazolinones, for inhibition of pathogenic processes related to **tissue trauma**)

IT **Gene**, animal
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(H19; **extracellular matrix**-regulating compds., including quinazolinones, for inhibition of pathogenic processes related to **tissue trauma**)

IT Proteins, specific or class
RL: BSU (Biological study, unclassified); BIOL (Biological study)

(HOX-D3, gene; **extracellular matrix**-regulating compds., including quinazolinones, for inhibition of pathogenic processes related to **tissue trauma**)

IT **Heat-shock proteins**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**HSP 47, HSP47; extracellular matrix**-regulating compds., including quinazolinones, for inhibition of pathogenic processes related to **tissue trauma**)

IT Insulin-like growth factor-binding proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(IGF-BP-6, gene; **extracellular matrix**-regulating compds., including quinazolinones, for inhibition of pathogenic processes related to **tissue trauma**)

IT Proteins, specific or class
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(MUTL, homolog, gene; **extracellular matrix**-regulating compds., including quinazolinones, for inhibition of pathogenic processes related to **tissue trauma**)

IT **Transcription factors**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**NF-.kappa.B (nuclear factor .kappa.B); extracellular matrix**-regulating compds., including quinazolinones, for inhibition of pathogenic processes related to **tissue trauma**)

IT Proteins, specific or class
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(RAD23, gene; **extracellular matrix**-regulating compds., including quinazolinones, for inhibition of pathogenic processes related to **tissue trauma**)

IT Proteins, specific or class
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(RAS-related protein RAB-5A, gene; **extracellular matrix**-regulating compds., including quinazolinones, for inhibition of pathogenic processes related to **tissue trauma**)

IT **Tumor necrosis factors**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**TNF-.alpha.; extracellular matrix**-regulating compds., including quinazolinones, for inhibition of pathogenic processes related to **tissue trauma**)

IT **Gene**, animal
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(Wnt-13; **extracellular matrix**-regulating compds., including quinazolinones, for inhibition of pathogenic processes related to **tissue trauma**)

IT **Connective tissue**
(adhesions; **extracellular matrix**-regulating compds., including quinazolinones, for inhibition of pathogenic processes related to **tissue trauma**)

IT **Transcription factors**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**cKrox; extracellular matrix**-regulating compds., including quinazolinones, for inhibition of pathogenic processes related to **tissue trauma**)

IT Bladder
(carcinoma, H19 gene expression; **extracellular matrix**-regulating compds., including quinazolinones, for inhibition of pathogenic processes related to **tissue trauma**)

IT Mammary gland
(carcinoma, integrin expression; **extracellular matrix**-regulating compds., including quinazolinones, for inhibition of pathogenic processes related to **tissue trauma**)

IT **Heart**, disease

(**cardiac fibrosis; extracellular matrix**-regulating compds., including quinazolinones, for inhibition of pathogenic processes related to **tissue trauma**)

IT Phosphoproteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(caveolins, 1, gene; **extracellular matrix**-regulating compds., including quinazolinones, for inhibition of pathogenic processes related to **tissue trauma**)

IT **Collagens, biological studies**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(collagen .alpha.1(I) gene; **extracellular matrix**-regulating compds., including quinazolinones, for inhibition of pathogenic processes related to **tissue trauma**)

IT **Gene**
(expression; **extracellular matrix**-regulating compds., including quinazolinones, for inhibition of pathogenic processes related to **tissue trauma**)

IT **Angiogenesis inhibitors**
Animal tissue
Anti-inflammatory agents
Antitumor agents
Cirrhosis
Drug delivery systems
Extracellular matrix
Fibrosis
Keloid
Psoriasis
Transcription, genetic
(**extracellular matrix**-regulating compds., including quinazolinones, for inhibition of pathogenic processes related to **tissue trauma**)

IT **Gene**, animal
Interleukin 1.beta.
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**extracellular matrix**-regulating compds., including quinazolinones, for inhibition of pathogenic processes related to **tissue trauma**)

IT **Kidney, disease**
Liver, disease
Lung, disease
(**fibrosis; extracellular matrix**-regulating compds., including quinazolinones, for inhibition of pathogenic processes related to **tissue trauma**)

IT CD59 (antigen)
Laminin receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gene; **extracellular matrix**-regulating compds., including quinazolinones, for inhibition of pathogenic processes related to **tissue trauma**)

IT **Skin, disease**
(hypertrophic **scar; extracellular matrix**-regulating compds., including quinazolinones, for inhibition of pathogenic processes related to **tissue trauma**)

IT CD antigens
Integrins
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(integrin .beta.5; **extracellular matrix**-regulating compds., including quinazolinones, for inhibition of pathogenic processes related to **tissue trauma**)

IT Proteins, specific or class
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(nuclear factor NF90, gene; **extracellular matrix**-regulating compds., including quinazolinones, for inhibition of pathogenic processes related to **tissue trauma**)

IT **Gene**, animal
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(rhoG; **extracellular matrix**-regulating compds., including quinazolinones, for inhibition of pathogenic processes related to **tissue trauma**)

IT Proteins, specific or class
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(transforming protein RHOA, gene; **extracellular matrix**-regulating compds., including quinazolinones, for inhibition of pathogenic processes related to **tissue trauma**)

IT Injury
(**trauma**; **extracellular matrix**-regulating compds., including quinazolinones, for inhibition of pathogenic processes related to **tissue trauma**)

IT Neoplasm
(tumor marker gene; **extracellular matrix**-regulating compds., including quinazolinones, for inhibition of pathogenic processes related to **tissue trauma**)

IT Integrins
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(.alpha.v; **extracellular matrix**-regulating compds., including quinazolinones, for inhibition of pathogenic processes related to **tissue trauma**)

IT Integrins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(.alpha.3, gene; **extracellular matrix**-regulating compds., including quinazolinones, for inhibition of pathogenic processes related to **tissue trauma**)

IT Transforming growth factors
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(.beta.-; **extracellular matrix**-regulating compds., including quinazolinones, for inhibition of pathogenic processes related to **tissue trauma**)

IT Integrins
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(.beta.3; **extracellular matrix**-regulating compds., including quinazolinones, for inhibition of pathogenic processes related to **tissue trauma**)

IT 9026-51-1
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(B, gene; **extracellular matrix**-regulating compds., including quinazolinones, for inhibition of pathogenic processes related to **tissue trauma**)

IT 11128-99-7, Angiotensin II
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(**extracellular matrix**-regulating compds., including quinazolinones, for inhibition of pathogenic processes related to **tissue trauma**)

IT 12766-00-6D, Quinazolinone, derivs. **55837-20-2, Halofuginone**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**extracellular matrix**-regulating compds., including quinazolinones, for inhibition of pathogenic processes related to **tissue trauma**)

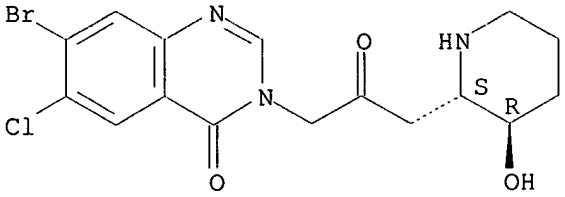
IT **9040-48-6, Collagenase type IV**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**extracellular matrix**-regulating compds., including quinazolinones, for inhibition of pathogenic processes related to **tissue trauma**)

IT 9001-50-7, Glyceraldehyde-3-phosphate dehydrogenase 124861-55-8, TIMP-2 140208-24-8, TIMP-1 169592-56-7, Apopain 182372-15-2
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gene; **extracellular matrix**-regulating compds.,

including quinazolinones, for inhibition of pathogenic processes related to **tissue trauma**)

IT **55837-20-2, Halofuginone**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**extracellular matrix**-regulating compds., including quinazolinones, for inhibition of pathogenic processes related to **tissue trauma**)
RN 55837-20-2 HCAPLUS
CN 4(3H)-Quinazolinone, 7-bromo-6-chloro-3-[3-[(2R,3S)-3-hydroxy-2-piperidinyl]-2-oxopropyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



IT **9040-48-6, Collagenase type IV**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**extracellular matrix**-regulating compds., including quinazolinones, for inhibition of pathogenic processes related to **tissue trauma**)
RN 9040-48-6 HCAPLUS
CN Gelatinase (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L145 ANSWER 10 OF 30 HCAPLUS COPYRIGHT 2001 ACS
AN 2000:54647 HCAPLUS
DN 132:73616
TI Topical treatment of cutaneous chronic graft versus host disease with **halofuginone** a novel inhibitor of collagen type I synthesis
AU **Nagler, Arnon; Pines, Mark**
CS Department of Bone Marrow Transplantation, Hadassah University Hospital, Jerusalem, Israel
SO Transplantation (**1999**), 68(11), 1806-1809
CODEN: TRPLAU; ISSN: 0041-1337
PB Lippincott Williams & Wilkins
DT Journal
LA English
CC **1-12** (Pharmacology)
AB Background. In chronic graft-vs.-host disease (cGvHD), skin **fibrosis**, contractures, and an increase in collagen content form the hallmark. We report a successful treatment of a cGvHD patient by topical application of **halofuginone**, an inhibitor of collagen .alpha.1(I) gene expression. Methods. **Halofuginone**-contg. ointment was applied daily on the left side of the neck and shoulder of a cGvHD patient. Collagen .alpha.1(I) gene expression and collagen content in skin biopsy specimens were evaluated by in situ hybridization and sirius red staining, resp. Results. After 3 and 6 mo, a marked redn. in skin collagen synthesis was obsd., accompanied with increase neck rotation on the treated side. After cessation of treatment, the sclerosis, skin tightness, and collagen .alpha.1(I) gene expression returned to baseline level. No adverse effects were obsd., and no plasma levels of **halofuginone** could be detected. Conclusions. **Halofuginone** may provide a promising novel and safe therapy for cGvHD patients.
ST skin graft vs host disease **halofuginone**; collagen I inhibitor **halofuginone** skin
IT Transplant and Transplantation
(graft-vs.-host reaction; collagen type I inhibitor

halofuginone for topical treatment of cutaneous chronic graft vs. host disease in humans)

IT **Collagens, biological studies**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(type I, inhibitors; collagen type I inhibitor **halofuginone** for topical treatment of cutaneous chronic graft vs. host disease in humans)

IT **55837-20-2, Halofuginone**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(collagen type I inhibitor **halofuginone** for topical treatment of cutaneous chronic graft vs. host disease in humans)

RE.CNT 9
RE
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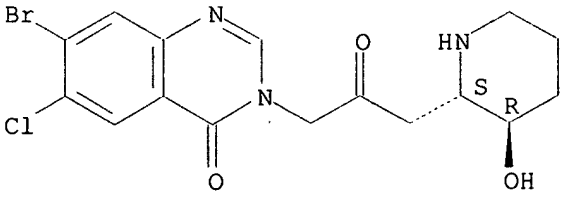
IT **55837-20-2, Halofuginone**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(collagen type I inhibitor **halofuginone** for topical treatment of cutaneous chronic graft vs. host disease in humans)

RN 55837-20-2 HCAPLUS
CN 4(3H)-Quinazolinone, 7-bromo-6-chloro-3-[3-[(2R,3S)-3-hydroxy-2-piperidinyl]-2-oxopropyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L145 ANSWER 11 OF 30 HCAPLUS COPYRIGHT 2001 ACS
AN 2000:44827 HCAPLUS
DN 132:329499
TI Inhibition of neovascularization and tumor growth, and facilitation of wound repair, by **halofuginone**, an inhibitor of collagen type I synthesis
AU Abramovitch, Rinat; Dafni, Hagit; Neeman, Michal; **Nagler, Arnon**; **Pines, Mark**
CS Department of Biological Regulation, The Weizmann Institute of Science, Rehovot, 76100, Israel
SO Neoplasia (N. Y.) (**1999**), 1(4), 321-329
CODEN: NEOPFL; ISSN: 1522-8002
PB Stockton Press
DT Journal
LA English
CC **1-6** (Pharmacology)
Section cross-reference(s): 14
AB **Halofuginone**, an inhibitor of collagen .alpha.1(I) gene expression was used for the treatment of s.c. implanted C6 glioma tumors. **Halofuginone** had no effect on the growth of C6 glioma spheroids in

vitro, and these spheroids showed no collagen .alpha.1(I) expression and no collagen synthesis. However, a significant attenuation of tumor growth was obsd. in vivo, for spheroids implanted in CD-1 nude mice which were treated by oral or i.p. (4 .mu.g every 48 h) administration of **halofuginone**. In these mice, treatment was assocd. with a dose-dependent redn. in collagen .alpha.1(I) expression and dose- and time-dependent inhibition of **angiogenesis**, as measured by MRI. Moreover, **halofuginone** treatment was assocd. with improved re-epithelialization of the chronic wounds that are assocd. with this exptl. model. Oral administration of **halofuginone** was effective also in intervention in tumor growth, and here, too, the treatment was assocd. with reduced **angiogenic** activity and vessel regression. These results demonstrate the important role of collagen type I in tumor **angiogenesis** and tumor growth and implicate its role in chronic wounds. Inhibition of the expression of collagen type I provides an attractive new target for cancer therapy.

ST **halofuginone** collagen tumor **angiogenesis** growth wound

IT Neuroglia
(glioma, inhibitors; inhibition of neovascularization and tumor growth, and facilitation of wound repair by **halofuginone**, inhibitor of collagen type I synthesis)

IT Antitumor agents
(glioma; inhibition of neovascularization and tumor growth, and facilitation of wound repair by **halofuginone**, inhibitor of collagen type I synthesis)

IT **Angiogenesis inhibitors**
Wound healing promoters
(inhibition of neovascularization and tumor growth, and facilitation of wound repair by **halofuginone**, inhibitor of collagen type I synthesis)

IT **Angiogenesis**
(neovascularization; inhibition of neovascularization and tumor growth, and facilitation of wound repair by **halofuginone**, inhibitor of collagen type I synthesis)

IT **Collagens, biological studies**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(type I; inhibition of neovascularization and tumor growth, and facilitation of wound repair by **halofuginone**, inhibitor of collagen type I synthesis)

IT **55837-20-2, Halofuginone**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of neovascularization and tumor growth, and facilitation of wound repair by **halofuginone**, inhibitor of collagen type I synthesis)

RE.CNT 34

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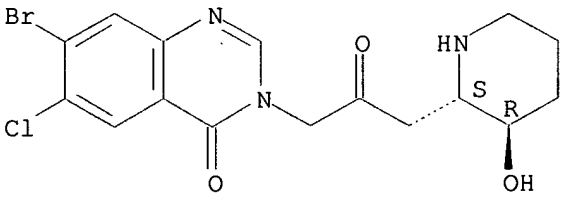
IT **55837-20-2, Halofuginone**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of neovascularization and tumor growth, and facilitation of wound repair by **halofuginone**, inhibitor of collagen type I synthesis)

RN 55837-20-2 HCAPLUS

CN 4(3H)-Quinazolinone, 7-bromo-6-chloro-3-[3-[(2R,3S)-3-hydroxy-2-piperidinyl]-2-oxopropyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L145 ANSWER 12 OF 30 HCAPLUS COPYRIGHT 2001 ACS

AN 1999:547687 HCAPLUS

DN 131:281130

TI Inhibition of bladder carcinoma **angiogenesis**, stromal support, and tumor growth by **halofuginone**

AU Elkin, Michael; Ariel, Ilana; Miao, Hua-Quan; **Nagler, Arnon**; **Pines, Mark**; De-Groot, Nathan; Hochberg, Avraham; **Vlodavsky, Israel**

CS Departments of Oncology, Hadassah-Hebrew University Hospital, Jerusalem, 91120, Israel

SO Cancer Res. (**1999**), 59(16), 4111-4118
CODEN: CNREA8; ISSN: 0008-5472

PB AACR Subscription Office

DT Journal

LA English

CC **1-6** (Pharmacology)

AB **Halofuginone**, a widely used alkaloid coccidiostat, is a potent inhibitor of collagen .alpha.1(I) and **matrix** metalloproteinase 2 gene expression. **Halofuginone** also suppresses **extracellular matrix** deposition and cell proliferation. We investigated the effects of **halofuginone** on transplantable and chem. induced mouse bladder carcinoma. In both systems, oral administration of **halofuginone** to male C3H/He mice resulted in a profound anticancerous effects, even when the treatment was initiated at advanced stages of tumor development. Although **halofuginone** failed to prevent proliferative preneoplastic alterations in the bladder epithelium, it inhibited further progression of the chem. induced tumor into a malignant invasive stage. Histol. examn. and in situ anal. of the tumor **tissue** revealed a marked decrease in blood vessel d. and

in both collagen .alpha.1(I) and H19 gene expression. H19 is regarded as an early marker of bladder carcinoma. The **antiangiogenic** effect of **halofuginone** was also demonstrated by inhibition of microvessel formation in vitro. We attribute the profound antitumoral effect of **halofuginone** to its combined inhibition of the tumor stromal support, vascularization, invasiveness, and cell proliferation.

ST **halofuginone** anticancer pharmacol bladder carcinoma

IT **Gene**, animal
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(H19; **halofuginone** inhibition of bladder carcinoma **angiogenesis**, stromal support and tumor growth in mice)

IT Bladder
(carcinoma; **halofuginone** inhibition of bladder carcinoma **angiogenesis**, stromal support and tumor growth in mice)

IT Antitumor agents
(**halofuginone** inhibition of bladder carcinoma **angiogenesis**, stromal support and tumor growth in mice)

IT **Collagens, biological studies**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**halofuginone** inhibition of bladder carcinoma **angiogenesis**, stromal support and tumor growth in mice)

IT **55837-20-2, Halofuginone**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(**halofuginone** inhibition of bladder carcinoma **angiogenesis**, stromal support and tumor growth in mice)

RE.CNT 46

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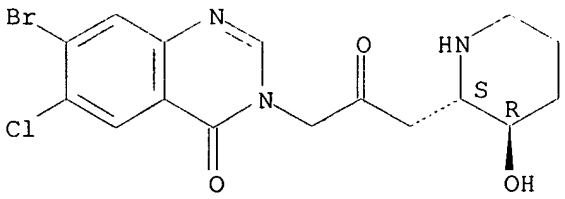
IT **55837-20-2, Halofuginone**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(**halofuginone** inhibition of bladder carcinoma **angiogenesis**, stromal support and tumor growth in mice)

RN 55837-20-2 HCAPLUS

CN 4(3H)-Quinazolinone, 7-bromo-6-chloro-3-[3-[(2R,3S)-3-hydroxy-2-piperidinyl]-2-oxopropyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L145 ANSWER 13 OF 30 HCAPLUS COPYRIGHT 2001 ACS

AN 1999:214468 HCAPLUS

DN 131:53977

TI **Halofuginone**, an inhibitor of collagen type I synthesis, prevents postoperative adhesion formation in the rat uterine horn model

AU **Nagler, Arnon**; Genina, Olga; Lavelin, Irina; Ohana, Meir; **Pines, Mark**

CS Department of Bone Marrow Transplantation, Hadassah University Hospital, Jerusalem, Israel

SO Am. J. Obstet. Gynecol. (**1999**), 180(3, Pt. 1), 558-563
CODEN: AJOGAH; ISSN: 0002-9378

PB Mosby, Inc.

DT Journal

LA English

CC **1-12** (Pharmacology)

AB The objective of this study was to evaluate the effects of **halofuginone**-a specific inhibitor of collagen type I synthesis-in preventing uterine horn adhesion formation in rats. Adhesions were induced by scraping the rat uterine horns until capillary bleeding occurred. **Halofuginone** was either injected i.p. or administered orally. The no. and severity of the adhesions were scored. Collagen .alpha.1(I) gene expression was evaluated by in situ hybridization; total collagen was estd. by sirius red staining. Collagen synthesis in response to **halofuginone** was evaluated in cells cultured from the adhesions. Regardless of the administration procedure, **halofuginone** reduced significantly the no. and severity of the adhesions in a dose-dependent manner. **Halofuginone** prevented the increase in collagen .alpha.1(I) gene expression obsd. in the rats that underwent this procedure, thus affecting only the newly synthesized collagen but not the resident collagen. In cells derived from rat uterine horn adhesions, **halofuginone** induced dose-dependent inhibition of collagen synthesis. Upregulation of collagen synthesis appears to play a crit. role in the pathophysiol. mechanism of adhesion formation. **Halofuginone** could be used as an important means of understanding the role of collagen in adhesion formation and might become a novel and promising **antifibrotic** agent for preventing adhesion formation

after pelvic surgery.
ST **antifibrotic halofuginone** collagen I synthesis inhibitor
IT **Connective tissue**
(disease, postoperative adhesion; **halofuginone** prevents postoperative adhesion formation in the rat uterine horn model)
IT **Fibrosis**
(inhibitor; **halofuginone** prevents postoperative adhesion formation in the rat uterine horn model)
IT **Collagens, biological studies**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(type I; **halofuginone** prevents postoperative adhesion formation in the rat uterine horn model)
IT **55837-20-2, Halofuginone**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**halofuginone** prevents postoperative adhesion formation in the rat uterine horn model)
RE.CNT 25
RE
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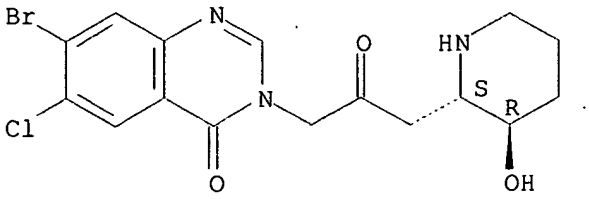
IT **55837-20-2, Halofuginone**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**halofuginone** prevents postoperative adhesion formation in the rat uterine horn model)
RN 55837-20-2 HCAPLUS
CN 4(3H)-Quinazolinone, 7-bromo-6-chloro-3-[3-[(2R,3S)-3-hydroxy-2-piperidinyl]-2-oxopropyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L145 ANSWER 14 OF 30 HCAPLUS COPYRIGHT 2001 ACS
AN 1998:776630 HCAPLUS
DN 130:20585
TI Treatment of hepatic **cirrhosis**
IN **Pines, Mark; Nagler, Arnon**
PA Hadasit Medical Research Services and Development, Israel; Agricultural Research Organization; Friedman, Mark, M.
SO PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K
CC **1-10** (Pharmacology)
Section cross-reference(s): **63**
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9852514	A2	19981126	WO 1998-US10505	19980522 <--
WO 9852514	A3	19990819		

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

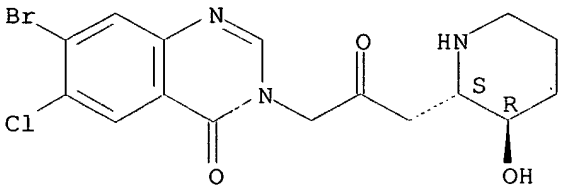
EP 1014988	A2	20000705	EP 1998-924847	19980522 <--

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI

PRAI US 1997-862382 A 19970523 <--
WO 1998-US10505 W 19980522 <--
OS MARPAT 130:20585
AB A compn. for treating hepatic **fibrosis** and hepatic **cirrhosis**, and methods of using and manufg. the compn. are provided. The compn. includes a quinazolinone deriv., preferably **halofuginone**. Examples are given showing the effect of **halofuginone** on histol. and morphol. of rat liver, effect of **halofuginone** on mild **fibrosis** in rat liver, inhibition of **fibrosis** induced by bile duct ligation, and suitable formulations for administration of **halofuginone**.
ST **halofuginone** hepatic **cirrhosis; fibrosis halofuginone**
IT **Liver cirrhosis**
Liver fibrosis
(**halofuginone** in treatment of hepatic **cirrhosis**)
IT **55837-20-2, Halofuginone**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**halofuginone** in treatment of hepatic **cirrhosis**)
IT **55837-20-2, Halofuginone**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**halofuginone** in treatment of hepatic **cirrhosis**)
RN 55837-20-2 HCAPLUS

CN 4(3H)-Quinazolinone, 7-bromo-6-chloro-3-[3-[(2R,3S)-3-hydroxy-2-piperidinyl]-2-oxopropyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



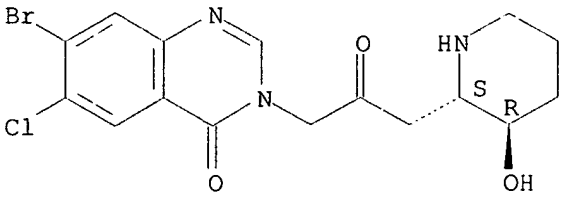
L145 ANSWER 15 OF 30 HCAPLUS COPYRIGHT 2001 ACS
AN 1998:682125 HCAPLUS
DN 129:254998
TI Treatment for pulmonary **fibrosis** with **Halofuginone** or other quinazolinone derivative
IN **Pines, Mark; Nagler, Arnon**
PA Agricultural Research Organization, Israel; Hadasit Medical Research Services and Development Co.
SO PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-505
CC **1-9** (Pharmacology)
Section cross-reference(s): **63**
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9843642	A1	19981008	WO 1997-IL115	19970331 <--
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9720420	A1	19981022	AU 1997-20420	19970331 <--
	AU 737094	B2	20010809		
	EP 991411	A1	20000412	EP 1997-908480	19970331 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	JP 2001518062	T2	20011009	JP 1997-525500	19970331 <--
PRAI	WO 1997-IL115	A	19970331 <--		

OS MARPAT 129:254998
AB A compn. for treating pulmonary **fibrosis** and a method of using and manufg. the compn. are provided. The compn. includes a quinazolinone deriv., preferably **Halofuginone**. The preferred method of administration is by inhalation, preferably with a pharmaceutically acceptable carrier in the form of an aerosol.
ST quinazolinone deriv pulmonary **fibrosis**; **Halofuginone** pulmonary **fibrosis**; aerosol quinazolinone deriv pulmonary **fibrosis**
IT Drug delivery systems
Pulmonary fibrosis
Sprays (drug delivery systems)
(**Halofuginone** or other quinazolinone deriv. for pulmonary **fibrosis** treatment)
IT **Collagens, biological studies**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**Halofuginone** or other quinazolinone deriv. for pulmonary

fibrosis treatment)
IT 11056-06-7, Bleomycin
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(**Halofuginone** or other quinazolinone deriv. for pulmonary **fibrosis** treatment)
IT **55837-20-2, Halofuginone**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**Halofuginone** or other quinazolinone deriv. for pulmonary **fibrosis** treatment)
IT 51-35-4, Hydroxyproline
RL: BOC (Biological occurrence); BPR (Biological process); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(**Halofuginone** or other quinazolinone deriv. for pulmonary **fibrosis** treatment)
IT **55837-20-2, Halofuginone**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**Halofuginone** or other quinazolinone deriv. for pulmonary **fibrosis** treatment)
RN 55837-20-2 HCAPLUS
CN 4(3H)-Quinazolinone, 7-bromo-6-chloro-3-[3-[(2R,3S)-3-hydroxy-2-piperidinyl]-2-oxopropyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L145 ANSWER 16 OF 30 HCAPLUS COPYRIGHT 2001 ACS
AN 1998:548536 HCAPLUS
DN 129:170522
TI Treatment and prevention of adhesions
IN **Pines, Mark; Nagler, Arnon**
PA Agricultural Research Organization, Ministry of Agriculture, Israel; Hadasit Medical Research Services and Development
SO PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-52
CC **1-7** (Pharmacology)
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9834617	A1	19980813	WO 1998-IL69	19980211 <--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5852024	A	19981222	US 1997-797701	19970211 <--
AU 9858776	A1	19980826	AU 1998-58776	19980211 <--
AU 737312	B2	20010816		
EP 996448	A1	20000503	EP 1998-902169	19980211 <--

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI

JP 2001511176 T2 20010807 JP 1998-534076 19980211 <--

PRAI US 1997-797701 A 19970211 <--

WO 1998-IL69 W 19980211 <--

OS MARPAT 129:170522

AB An inhibitor of adhesion formation which can be used to prevent adhesions within the abdominal cavity, particularly following surgical intervention in the area. Specifically, the most preferred compd. of the present invention, **Halofuginone**, can be used to prevent collagen deposition from occurring within the peritoneum after such surgical intervention, thereby inhibiting adhesion formation. **Halofuginone**, and related compds., are useful in the prevention and treatment of both **inflammatory** and surgically induced adhesions, and in the treatment of congenital adhesions. Examples are given for involvement of collagen in adhesion formation, effect of **halofuginone** on collagen gene expression and content and **halofuginone** effect on adhesion no.

ST **halofuginone** adhesion prevention; **inflammation** inhibitor **halofuginone**

IT Reproductive tract diseases
(adnexitis; **halofuginone** for adhesion prevention and treatment of **inflammation**)

IT **Adhesion (biological)**
Anti-inflammatory drugs
Antibiotics
Wound healing promoters
(**halofuginone** for adhesion prevention and treatment of **inflammation**)

IT **Collagens, biological studies**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**halofuginone** for adhesion prevention and treatment of **inflammation**)

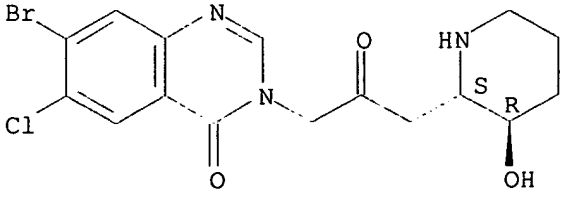
IT **55837-20-2, Halofuginone**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**halofuginone** for adhesion prevention and treatment of **inflammation**)

IT **55837-20-2, Halofuginone**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**halofuginone** for adhesion prevention and treatment of **inflammation**)

RN 55837-20-2 HCAPLUS

CN 4(3H)-Quinazolinone, 7-bromo-6-chloro-3-[3-[(2R,3S)-3-hydroxy-2-piperidinyl]-2-oxopropyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L145 ANSWER 17 OF 30 HCAPLUS COPYRIGHT 2001 ACS

AN 1998:548535 HCAPLUS

DN 129:170544

TI Treatment of skin disorders with **Halofuginone** and related compounds

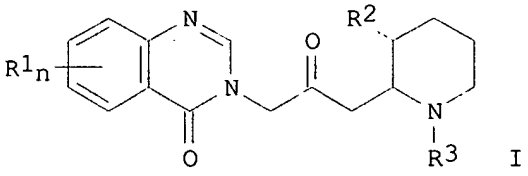
IN **Pines, Mark; Nagler, Arnon**

PA Agricultural Research Organization, Ministry of Agriculture, Israel;

Hadasit Medical Research Services and Development Company Ltd.
SO PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-505
CC **1-12** (Pharmacology)
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9834616	A1	19980813	WO 1998-IL71	19980211 <--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 6211188	B1	20010403	US 1997-797702	19970211 <--
AU 9860050	A1	19980826	AU 1998-60050	19980211 <--
EP 1019054	A1	20000719	EP 1998-903276	19980211 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2001511177	T2	20010807	JP 1998-534078	19980211 <--

PRAI US 1997-797702 A 19970211 <--
WO 1998-IL71 W 19980211 <--
OS MARPAT 129:170544
GI



I

AB An effective treatment for skin disorders characterized by abnormal skin cell behavior, the treatment including a pharmaceutically effective amt. of I (R1 = H, halo, nitro, benzo, lower alkyl, Ph, lower alkoxy; R2 = OH, acetoxy, lower alkoxy; R3 = H, lower alkenoxy), esp. **Halofuginone** and pharmaceutically acceptable salts thereof. Skin disorders which can be treated include **keloids**, hypertrophic **scars**, **psoriasis**, acne, seborrhea and alopecia. **Halofuginone** can reduce or eliminate clin. symptoms of these disorders, as well as substantially prevent the formation of **keloids** and hypertrophic **scars**.

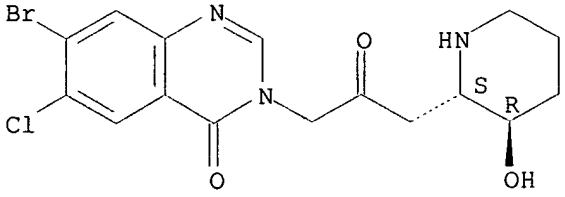
ST **Halofuginone** skin disorder treatment; **keloid** hypertrophic **scar Halofuginone; psoriasis** acne seborrhea alopecia **Halofuginone**

IT **Acne**
Alopecia
Extracellular matrix
Keloid
Psoriasis
Seborrhea
Skin diseases
(**Halofuginone** and related compds. for skin disorder treatment)

IT **Collagens, biological studies**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**Halofuginone** and related compds. for skin disorder treatment)

IT **Genes** (animal)
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(collagen .alpha.1(I); **Halofuginone** and related compds. for skin disorder treatment)
IT Mesangial cell (renal)
Vascular endothelium
(**extracellular matrix**; **Halofuginone** and related compds. for skin disorder treatment)
IT **Skin diseases**
(hypertrophic **scar**; **Halofuginone** and related compds. for skin disorder treatment)
IT Surgery
(**keloid**-like growth from; **Halofuginone** and related compds. for skin disorder treatment)
IT **Adhesion (biological)**
(surgical adhesions; **Halofuginone** and related compds. for skin disorder treatment)
IT **55837-20-2, Halofuginone**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**Halofuginone** and related compds. for skin disorder treatment)
IT **55837-20-2, Halofuginone**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**Halofuginone** and related compds. for skin disorder treatment)
RN 55837-20-2 HCAPLUS
CN 4(3H)-Quinazolinone, 7-bromo-6-chloro-3-[3-[(2R,3S)-3-hydroxy-2-piperidinyl]-2-oxopropyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

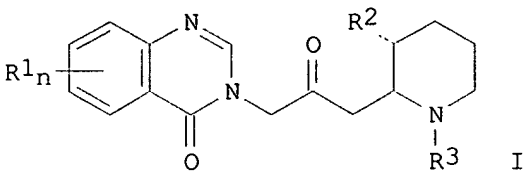


L145 ANSWER 18 OF 30 HCAPLUS COPYRIGHT 2001 ACS
AN 1998:548532 HCAPLUS
DN 129:170518
TI Quinazolinone-containing pharmaceutical compositions for prevention of neovascularization and for treating malignancies
IN **Pines, Mark**; **Nagler, Arnon**; **Vlodavsky, Israel**
; Miao, Hua-Quan
PA Agricultural Research Organization, Israel; Hadasit Medical Research Services and Development Company Ltd.
SO PCT Int. Appl., 79 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-445
ICS A61K031-505
CC **1-6** (Pharmacology)
Section cross-reference(s): **63**
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9834613	A1	19980813	WO 1998-IL70	19980211 <--

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC,

LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT,
RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, AM,
AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI,
FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM,
GA, GN, ML, MR, NE, SN, TD, TG
US 6028075 A 20000222 US 1997-797703 19970211 <--
AU 9860049 A1 19980826 AU 1998-60049 19980211 <--
EP 1007044 A1 20000614 EP 1998-903275 19980211 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, FI
JP 2001518075 T2 20011009 JP 1998-534077 19980211 <--
PRAI US 1997-797703 A 19970211 <--
WO 1998-IL70 W 19980211 <--
OS MARPAT 129:170518
GI



I

AB Compns. are provided for attenuating neovascularization and treating malignancies. The compns. include a pharmaceutically effective amt. of I (R1 = H, halo, nitro, benzo, lower alkyl, Ph, lower alkoxy; R2 = OH, acetoxy, lower alkoxy; and R3 = H, lower alkenoxy carbonyl), and pharmaceutically acceptable salts thereof, in combination with a pharmaceutically acceptable carrier. Compds. of the invention include **Halofuginone** and pharmaceutically acceptable salts thereof.

ST cancer treatment neovascularization inhibition quinazolinone deriv; **Halofuginone** cancer treatment neovascularization inhibition

IT **Genes** (animal)
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(H19; quinazolinone-contg. pharmaceutical compns. for prevention of neovascularization and for treatment of malignancies)

IT Prostatic carcinoma inhibitors
(adenocarcinoma; quinazolinone-contg. pharmaceutical compns. for prevention of neovascularization and for treatment of malignancies)

IT Glioma inhibitors
(astrocytoma inhibitors; quinazolinone-contg. pharmaceutical compns. for prevention of neovascularization and for treatment of malignancies)

IT Squamous cell carcinoma inhibitors
(cervical squamous cell carcinoma inhibitors; quinazolinone-contg. pharmaceutical compns. for prevention of neovascularization and for treatment of malignancies)

IT **Genes** (animal)
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(collagen type I; quinazolinone-contg. pharmaceutical compns. for prevention of neovascularization and for treatment of malignancies)

IT Antitumor agents
Histiocyte
(**fibrous** histiocytoma inhibitors; quinazolinone-contg. pharmaceutical compns. for prevention of neovascularization and for treatment of malignancies)

IT **Type I collagen**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gene; quinazolinone-contg. pharmaceutical compns. for prevention of neovascularization and for treatment of malignancies)

IT Sarcoma inhibitors
Vascular tumors
(hemangiosarcoma inhibitors; quinazolinone-contg. pharmaceutical

compns. for prevention of neovascularization and for treatment of malignancies)

IT Breast carcinoma inhibitors
(infiltrating ductal; quinazolinone-contg. pharmaceutical compns. for prevention of neovascularization and for treatment of malignancies)

IT Astrocytoma
Pancreatic adenocarcinoma
Rhabdomyosarcoma
Skin tumors
(inhibitors; quinazolinone-contg. pharmaceutical compns. for prevention of neovascularization and for treatment of malignancies)

IT CD antigens
Integrins
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(integrin .beta.5; quinazolinone-contg. pharmaceutical compns. for prevention of neovascularization and for treatment of malignancies)

IT Sarcoma inhibitors
(leiomyosarcoma inhibitors; quinazolinone-contg. pharmaceutical compns. for prevention of neovascularization and for treatment of malignancies)

IT Myoma
(leiomyosarcoma, inhibitors; quinazolinone-contg. pharmaceutical compns. for prevention of neovascularization and for treatment of malignancies)

IT Adenocarcinoma inhibitors
(pancreatic; quinazolinone-contg. pharmaceutical compns. for prevention of neovascularization and for treatment of malignancies)

IT Adenocarcinoma inhibitors
(prostatic; quinazolinone-contg. pharmaceutical compns. for prevention of neovascularization and for treatment of malignancies)

IT **Angiogenesis inhibitors**
Antiproliferative agents
Antitumor agents
Apoptosis
Bladder carcinoma inhibitors
Breast carcinoma inhibitors
Breast tumor inhibitors
Cell migration
Colon adenocarcinoma inhibitors
Drug delivery systems
Extracellular matrix
Glioma inhibitors
Hepatoma inhibitors
Lung tumor inhibitors
Melanoma inhibitors
Mesangial cell (renal)
Metastasis inhibitors
Neovascularization
Ovarian tumor inhibitors
Sarcoma inhibitors
Vascular endothelium
(quinazolinone-contg. pharmaceutical compns. for prevention of neovascularization and for treatment of malignancies)

IT Integrin .alpha.v
Integrin .beta.3
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(quinazolinone-contg. pharmaceutical compns. for prevention of neovascularization and for treatment of malignancies)

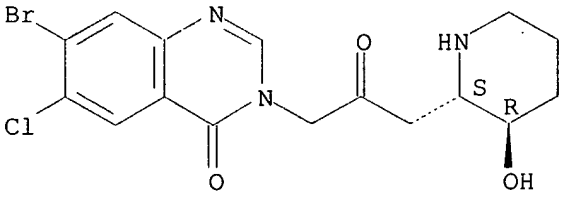
IT Sarcoma inhibitors
(rhabdomyosarcoma; quinazolinone-contg. pharmaceutical compns. for prevention of neovascularization and for treatment of malignancies)

IT Antitumor agents
(skin; quinazolinone-contg. pharmaceutical compns. for prevention of neovascularization and for treatment of malignancies)

IT Cervical tumor inhibitors
(squamous cell carcinoma inhibitors; quinazolinone-contg. pharmaceutical compns. for prevention of neovascularization and for

treatment of malignancies)
IT **55837-20-2, Halofuginone**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(quinazolinone-contg. pharmaceutical compns. for prevention of neovascularization and for treatment of malignancies)
IT 146480-35-5, MMP 2
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(quinazolinone-contg. pharmaceutical compns. for prevention of neovascularization and for treatment of malignancies)
IT **55837-20-2, Halofuginone**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(quinazolinone-contg. pharmaceutical compns. for prevention of neovascularization and for treatment of malignancies)
RN 55837-20-2 HCAPLUS
CN 4(3H)-Quinazolinone, 7-bromo-6-chloro-3-[3-[(2R,3S)-3-hydroxy-2-piperidinyl]-2-oxopropyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L145 ANSWER 19 OF 30 HCAPLUS COPYRIGHT 2001 ACS
AN 1998:385487 HCAPLUS
DN 129:45344
TI Intracoronary stents containing quinazolinone derivatives
IN Davidson, Clifford M.; **Nagler, Arnon**; Slavin, Shimon; **Hazum, Eli**; **Vlodavsky, Israel**; Geller, Ehud; **Pines, Mark**
PA Agricultural Research Organization Ministry of Agriculture, Israel; Hadasit Medical Research Services & Development Company Ltd.; Davidson, Clifford M.; Nagler, Arnon; Slavin, Shimon; Hazum, Eli; Vlodavsky, Israel; Geller, Ehud; Pines, Mark
SO PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K
CC **63-7** (Pharmaceuticals)
FAN.CNT 3

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9823244	A2	19980604	WO 1997-US15254	19970814 <--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
IL 119162	A1	20000629	IL 1996-119162	19960830 <--
AU 9867559	A1	19980622	AU 1998-67559	19970814 <--
AU 712520	B2	19991111		
CN 1219125	A	19990609	CN 1997-194218	19970814 <--
EP 936910	A2	19990825	EP 1997-954887	19970814 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,				

	IE, FI					
	JP 2001500040	T2	20010109		JP 1998-520852	19970814 <--
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PRAI	IL 1996-119162	A	19960830	<--		
	IL 1994-110831	A0	19940831	<--		
	WO 1997-US15254	W	19970814	<--		
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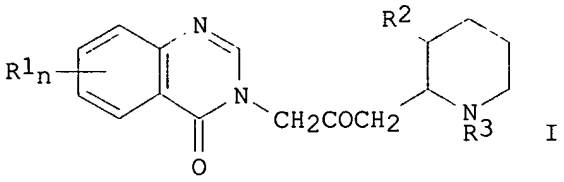
OS MARPAT 129:45344

GI



I

AB An intracoronary stent coated with a quinazolinone deriv. (I; n = 1, 2; R1 = H, halo, NO2, benzo, lower alkyl, Ph, lower alkoxy; R2 = OH, OAc, lower alkoxy; R3 = H, lower alkenoxycarbonyl) and physiol. acceptable salts thereof is useful for preventing restenosis after angioplasty. Thus, **halofuginone** (75 or 125 ng/mL) inhibited proliferation of bovine aortic smooth muscle cells and 3T3 **fibroblasts** and transiently inhibited proliferation of bovine aortic endothelial cells in vitro.

ST artery stent restenosis quinazolinone; coronary smooth muscle proliferation quinazolinone

IT Drug delivery systems
(films; intracoronary stents contg. quinazolinone derivs.)

IT Arterial injury
Coatings
Coronary artery restenosis
Fibroblast
Stents
(intracoronary stents contg. quinazolinone derivs.)

IT Proliferation inhibition
(of coronary smooth muscle cells; intracoronary stents contg. quinazolinone derivs.)

IT **Artery endothelium**
(proliferation of cells of coronary; intracoronary stents contg. quinazolinone derivs.)

IT **Vascular smooth muscle**
(proliferation of cells of; intracoronary stents contg. quinazolinone derivs.)

IT 24937-78-8, Ethylene/vinyl acetate copolymer
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(coating, **halofuginone**-contg.; intracoronary stents contg. quinazolinone derivs.)

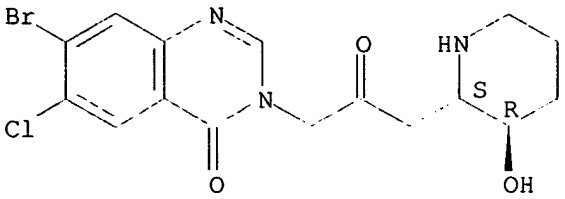
IT 491-36-1D, Quinazolin-4-one, derivs. **55837-20-2, Halofuginone**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(intracoronary stents contg. quinazolinone derivs.)

IT **55837-20-2, Halofuginone**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(intracoronary stents contg. quinazolinone derivs.)

RN 55837-20-2 HCAPLUS

CN 4(3H)-Quinazolinone, 7-bromo-6-chloro-3-[3-[(2R,3S)-3-hydroxy-2-piperidinyl]-2-oxopropyl]-, rel- (9CI) (CA INDEX NAME)

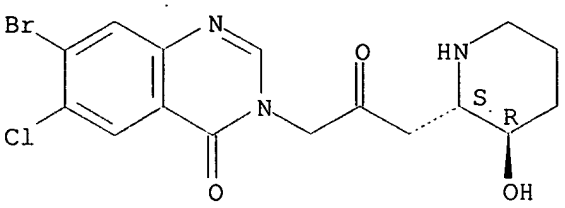
Relative stereochemistry.



L145 ANSWER 20 OF 30 HCAPLUS COPYRIGHT 2001 ACS
AN 1998:169290 HCAPLUS
DN 128:278527
TI **Halofuginone**: a novel **antifibrotic** therapy
AU **Pines, M.; Nagler, A.**
CS The Volcani Center, Institute of Animal Science, Agricultural Research Organization, Bet Dagan, 50250, Israel
SO Gen. Pharmacol. (**1998**), 30(4), 445-450
CODEN: GEPHDP; ISSN: 0306-3623
PB Elsevier Science Inc.
DT Journal; General Review
LA English
CC **1-0** (Pharmacology)
AB A review with .apprx.60 refs. 1. **Fibrosis** is characterized by **extracellular matrix** deposition, of which collagen type I is the major constituent. The progressive accumulation of connective **tissue** resulted in destruction of normal **tissue** architecture and function. 2. **Fibrosis** is a common response to various insults or injuries and can be the outcome of any perturbation in the cellular function of any **tissue**. 3. **Halofuginone** was found to inhibit collagen .alpha.1(I) gene expression and collagen synthesis in a variety of cell cultures including human **fibroblasts** derived from patients with excessive skin collagen type I synthesis. 4. **Halofuginone** was found to inhibit collagen .alpha.1(I) gene expression and collagen synthesis in animal models characterized by excessive deposition of collagen. In these models, **fibrosis** was induced in various **tissues** such as skin, liver, lung, etc. **Halofuginone** was injected i.p., added to the foodstuff or applied locally. 5. **Halofuginone** decreased skin collagen in a chronic graft-vs.-host disease patient. 6. The ability of extremely low concns. of **halofuginone** to inhibit collagen .alpha.1(I) synthesis specifically and transiently at the transcriptional level suggests that this material fulfills the criteria for a successful and effective anti-**fibrotic** therapy.
ST review **fibrosis** therapy **halofuginone**
IT **Fibrosis**
Transcription (genetic)
(**antifibrotic** therapy with **halofuginone** and inhibition of collagen .alpha.1(I) gene expression)
IT **Type I collagen**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**antifibrotic** therapy with **halofuginone** and inhibition of collagen .alpha.1(I) gene expression)
IT **55837-20-2, Halofuginone**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**antifibrotic** therapy with **halofuginone** and inhibition of collagen .alpha.1(I) gene expression)
IT **55837-20-2, Halofuginone**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**antifibrotic** therapy with **halofuginone** and inhibition of collagen .alpha.1(I) gene expression)
RN 55837-20-2 HCAPLUS
CN 4(3H)-Quinazolinone, 7-bromo-6-chloro-3-[3-[(2R,3S)-3-hydroxy-2-

piperidinyl]-2-oxopropyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L145 ANSWER 21 OF 30 HCAPLUS COPYRIGHT 2001 ACS
AN 1997:806407 HCAPLUS
DN 128:110646
TI Inhibition of glomerular mesangial cell proliferation and **extracellular matrix** deposition by **halofuginone**
AU **Nagler, Arnon**; Katz, Avi; Aingorn, helena; Miao, Hua-Quan; Condiotti, Reba; Genina, Olga; **Pines, Mark**; **Vlodavsky, Israel**
CS Dep. of Bone-Marrow Transplantation, Hadassah-Hebrew Univ. Hosp., Jerusalem, Israel
SO Kidney Int. (**1997**), 52(6), 1561-1569
CODEN: KDYIA5; ISSN: 0085-2538
PB Blackwell Science, Inc.
DT Journal
LA English
CC **1-8** (Pharmacology)
AB Mesangial cell proliferation, increased deposition of collagen, and expansion of the mesangial **extracellular matrix** (ECM) are key features in the development of mesangioproliferative diseases. **Halofuginone**, a low mol. wt. anti-coccidial quinoazolinone deriv., inhibits collagen type .alpha.1(I) gene expression and synthesis. We investigated the effect of **halofuginone** on both normal and SV40 transformed mesangial cell proliferation, collagen synthesis, and ECM deposition. Proliferation of both cell types was almost completely inhibited in the presence of 50 ng/mL **halofuginone**. The cells were arrested in the late G1 phase of the cell cycle and resumed their normal growth rate following removal of the compd. from the culture medium. The antiproliferative effect of **halofuginone** was assocd. with inhibition of tyrosine phosphorylation of cellular proteins. Similar results were obtained whether the mesangial cells were seeded on regular **tissue** culture plastic or in close contact with a naturally produced ECM resembling their local environment in vivo. **Halofuginone** also inhibited synthesis and deposition of ECM by mesangial cells as indicated by a substantial redn. in 14C-glycine and Na235SO4 incorporation into the ECM, and by the inhibition of collagen type I synthesis and gene expression. It is proposed that by inhibiting collagen type I synthesis and **matrix** deposition, **halofuginone** exerts a potent antiproliferative effect that may be applied to inhibit mesangial cell proliferation and **matrix** expansion in a variety of chronic progressive glomerular diseases.
ST **halofuginone** mesangium collagen mesangioproliferative glomerular disease
IT **Genes** (animal)
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(for collagen; **halofuginone** inhibition of glomerular mesangial cell proliferation and **extracellular matrix** deposition)
IT Mesangial cell (renal)
Protein phosphorylation
(**halofuginone** inhibition of glomerular mesangial cell proliferation and **extracellular matrix** deposition)
IT **Type I collagen**

RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**halofuginone** inhibition of glomerular mesangial cell proliferation and **extracellular matrix** deposition)

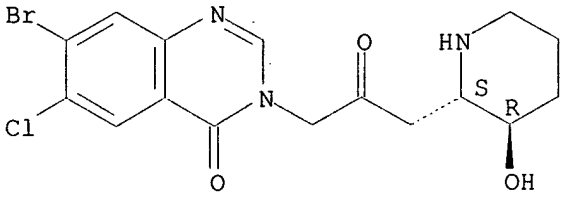
IT Glomerular diseases
(mesangioproliferative; **halofuginone** inhibition of glomerular mesangial cell proliferation and **extracellular matrix** deposition)

IT **55837-20-2, Halofuginone**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**halofuginone** inhibition of glomerular mesangial cell proliferation and **extracellular matrix** deposition)

IT **55837-20-2, Halofuginone**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**halofuginone** inhibition of glomerular mesangial cell proliferation and **extracellular matrix** deposition)

RN 55837-20-2 HCAPLUS
CN 4(3H)-Quinazolinone, 7-bromo-6-chloro-3-[3-[(2R,3S)-3-hydroxy-2-piperidinyl]-2-oxopropyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L145 ANSWER 22 OF 30 HCAPLUS COPYRIGHT 2001 ACS
AN 1997:592832 HCAPLUS
DN 127:257573
TI **Halofuginone**, a specific inhibitor of collagen type I synthesis, prevents dimethylnitrosamine-induced liver **cirrhosis**
AU **Pines, Mark**; Knopov, Viktor; Genina, Olga; Lavelin, Irina; **Nagler, Arnon**
CS The Volcani Center, Institute of Animal Science, Agricultural Research Organization, Bet Dagan, 50250, Israel
SO J. Hepatol. (**1997**) 27(2), 391-398
CODEN: JOHEEC; ISSN: 0168-8278
PB Munksgaard
DT Journal
LA English
CC **1-12** (Pharmacology)
Section cross-reference(s): 14
AB Hepatic **cirrhosis** is characterized by excessive deposition of collagen, resulting from an increase in type I collagen gene transcription. The authors evaluated the effect of **halofuginone** - a specific inhibitor of collagen type .alpha.1(I) gene expression - on dimethylnitrosamine (DMN)-induced liver **fibrosis/cirrhosis** in rats. **Fibrosis** was induced by i.p. injection of DMN. **Halofuginone** (5 mg/kg) was added to the diet. Collagen was stained with Sirius red and collagen .alpha.1(I) gene expression was evaluated by in situ hybridization. In control rats, a low level of collagen .alpha.1(I) gene expression was obsd. A high dose of DMN (1%) caused severe **fibrosis**, as indicated by induction of collagen .alpha.1(I) gene expression and increased liver collagen content. Addn. of **halofuginone** before the onset of **fibrosis**, almost completely prevented the increase in collagen type I gene expression and resulted in lower liver collagen content. Moreover, **halofuginone** partially prevented the marked decrease in liver wt. and reduced the mortality rate. At a lower dose of DMN (0.25%), which

causes mild **fibrosis, halofuginone** prevented the increase in collagen .alpha.1(I) gene expression, prevented the increase in liver collagen deposition and reduced plasma alk. phosphatase activity, all of which are characteristic of liver **fibrosis/cirrhosis**. These results suggest that **halofuginone** can be used as an important tool to understand the regulation of the collagen .alpha.1(I) gene and may become a novel and promising **antifibrotic** agent for liver **fibrosis/cirrhosis**.

ST **halofuginone** collagen synthesis inhibitor liver **cirrhosis**

IT **Cirrhosis (liver)**
Hepatoprotectants
(specific inhibitor of collagen type I synthesis **halofuginone** prevents methylnitrosamine-induced liver **cirrhosis**)

IT **Genes** (animal)
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(type I collagen .alpha.1 chain-encoding; specific inhibitor of collagen type I synthesis **halofuginone** prevents methylnitrosamine-induced liver **cirrhosis**)

IT **Type I collagen**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(.alpha.1 chain, gene encoding; specific inhibitor of collagen type I synthesis **halofuginone** prevents methylnitrosamine-induced liver **cirrhosis**)

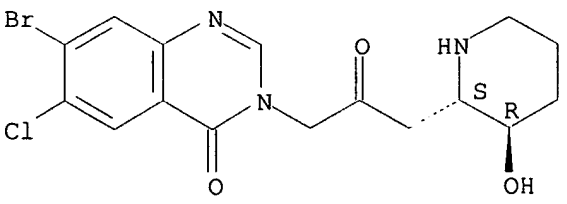
IT **55837-20-2, Halofuginone**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(specific inhibitor of collagen type I synthesis **halofuginone** prevents methylnitrosamine-induced liver **cirrhosis**)

IT **55837-20-2, Halofuginone**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(specific inhibitor of collagen type I synthesis **halofuginone** prevents methylnitrosamine-induced liver **cirrhosis**)

RN 55837-20-2 HCAPLUS

CN 4(3H)-Quinazolinone, 7-bromo-6-chloro-3-[3-[(2R,3S)-3-hydroxy-2-piperidinyl]-2-oxopropyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L145 ANSWER 23 OF 30 HCAPLUS COPYRIGHT 2001 ACS

AN 1997:234342 HCAPLUS

DN 126:220711

TI Quinazolinone-containing pharmaceutical compositions for prevention of neovascularization and for treating human malignancies

IN **Nagler, Aron**; Slavin, Shimon; **Vlodavsky, Israel**; **Pines, Mark**

PA Davidson, Clifford, M., USA; Agricultural Research Organization, Ministry of Agricultural; Hadasit Medical Research Services and Development Co; Nagler, Aron; Slavin, Shimon; Vlodavsky, Israel; Pines, Mark

SO PCT Int. Appl., 38 pp.
CODEN: PIXXD2

DT Patent

LA English

IC ICM A61K031-505

CC **1-8** (Pharmacology)
Section cross-reference(s): **63**

FAN.CNT 1

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PI	WO 9706805	A1	19970227	WO 1996-US13210	19960812 <--
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	CA 2228524	AA	19970227	CA 1996-2228524	19960812 <--
	AU 9668469	A1	19970312	AU 1996-68469	19960812 <--
	AU 705955	B2	19990603		
	EP 850062	A1	19980701	EP 1996-928874	19960812 <--
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	US 6090814	A	20000718	US 1998-11696	19980526 <--
PRAI	IL 1995-114951	A	19950815 <--		
	WO 1996-US13210	W	19960812 <--		

OS MARPAT 126:220711

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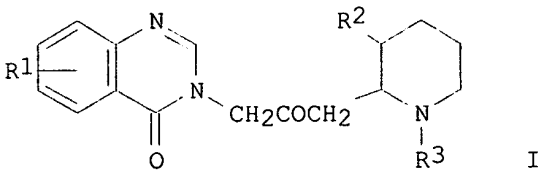


I

AB The invention provides a compn. for attenuating neovascularization and treating human malignancies, including a pharmaceutically effective amt. of a compd. of formula (I), wherein R1 is a member of the group consisting of hydrogen, halogen, nitro, benzo, lower alkyl, Ph and lower alkoxy; R2 is a member of the group consisting of hydroxy, acetoxy and lower alkoxy; and R3 is a member of the group consisting of hydrogen and lower alkenoxy-carbonyl; as active ingredient therein, in combination with a pharmaceutically acceptable carrier.

ST quinazolinone neovascularization prevention malignancies treatment; **angiogenesis** inhibitor quinazolinone antitumor agent

IT **Angiogenesis inhibitors**
Antitumor agents
(quinazolinone-contg. pharmaceutical compns. for prevention of neovascularization and for treating human malignancies)

IT **55837-20-2, Halofuginone**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(quinazolinone-contg. pharmaceutical compns. for prevention of neovascularization and for treating human malignancies)

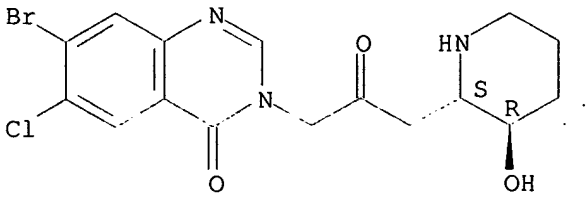
IT **55837-20-2, Halofuginone**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(quinazolinone-contg. pharmaceutical compns. for prevention of neovascularization and for treating human malignancies)

RN 55837-20-2 HCAPLUS

CN 4(3H)-Quinazolinone, 7-bromo-6-chloro-3-[3-[(2R,3S)-3-hydroxy-2-

piperidinyl]-2-oxopropyl]-, rel- (9CI) (CA INDEX NAME)

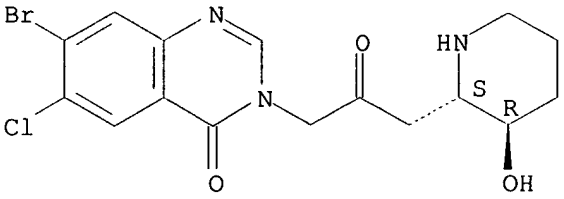
Relative stereochemistry.



L145 ANSWER 24 OF 30 HCAPLUS COPYRIGHT 2001 ACS
AN 1997:115504 HCAPLUS
DN 126:166280
TI Inhibition of collagen synthesis, smooth muscle cell proliferation, and injury-induced intimal hyperplasia by **halofuginone**
AU **Nagler, Arnon**; Miao, Hua-Quan; Aingorn, Helena; **Pines, Mark**; Genina, Olga; **Vlodavsky, Israel**
CS Department of Bone Marrow Transplantation, Hadassah-Hebrew University Hospital, Jerusalem, Israel
SO Arterioscler., Thromb., Vasc. Biol. (**1997**), 17(1), 194-202
CODEN: ATVBFA; ISSN: 1079-5642
PB American Heart Association
DT Journal
LA English
CC **1-8** (Pharmacology)
AB Proliferation of vascular smooth muscle cells (SMCs) and accumulation of **extracellular matrix** (ECM) components within the arterial wall in response to local injury are important etiol. factors in vascular proliferative disorders such as arteriosclerosis and restenosis after angioplasty. Fibrillar and nonfibrillar collagens are major constituents of the ECM that modulate cell shape and proliferative responses and thereby contribute to the pathogenesis of intimal hyperplasia. **Halofuginone**, an anticoccidial quinoazolinone deriv., inhibits collagen type I gene expression. We investigated the effect of **halofuginone** on (1) proliferation of bovine aortic endothelial cells and SMCs derived from the same specimen and maintained in vitro, (2) ECM deposition and collagen type I synthesis and gene expression, and (3) injury-induced intimal hyperplasia in vivo. DNA synthesis and proliferation of vascular SMCs in response to serum or basic **fibroblast** growth factor were abrogated in the presence of as little as 0.1 .mu.g/mL **halofuginone**; this inhibition was reversible upon removal of the compd. Under the same conditions, **halofuginone** exerted a relatively small antiproliferative effect on the resp. vascular endothelial cells. **Halofuginone** also inhibited the synthesis and deposition of ECM components by vascular SMCs as indicated both by a substantial redn. in the amt. of sulfated proteoglycans and collagen type I synthesis and gene expression. Local administration of **halofuginone** in the rabbit ear model of crush injury-induced arterial intimal hyperplasia resulted in a 50% redn. in intimal thickening as measured by a morphometric anal. of the neointima/media ratio. The differential inhibitory effect of **halofuginone** on vascular SMCs vs. endothelial cells, its inhibition of ECM deposition and collagen type I synthesis, and its ability to attenuate injury-induced intimal hyperplasia may place **halofuginone** alone or in combination with other antiproliferative compds. as a potential candidate for prevention of arterial stenosis and accelerated atherosclerosis.
ST collagen artery proliferation injury **halofuginone** antiatherosclerotic
IT **Vascular endothelium**
(artery; inhibition of collagen synthesis, smooth muscle cell proliferation, and injury-induced intimal hyperplasia by

halofuginone)
IT **Artery**
(endothelium; inhibition of collagen synthesis, smooth muscle cell proliferation, and injury-induced intimal hyperplasia by **halofuginone**)
IT Antiatherosclerotics
Arterial intimal hyperplasia
Cell proliferation
DNA formation
Extracellular matrix
(inhibition of collagen synthesis, smooth muscle cell proliferation, and injury-induced intimal hyperplasia by **halofuginone**)
IT **Genes** (animal)
Sulfated proteoglycans
Type I collagen
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(inhibition of collagen synthesis, smooth muscle cell proliferation, and injury-induced intimal hyperplasia by **halofuginone**)
IT **55837-20-2, Halofuginone**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of collagen synthesis, smooth muscle cell proliferation, and injury-induced intimal hyperplasia by **halofuginone**)
IT **55837-20-2, Halofuginone**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of collagen synthesis, smooth muscle cell proliferation, and injury-induced intimal hyperplasia by **halofuginone**)
RN 55837-20-2 HCAPLUS
CN 4(3H)-Quinazolinone, 7-bromo-6-chloro-3-[3-[(2R,3S)-3-hydroxy-2-piperidinyl]-2-oxopropyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L145 ANSWER 25 OF 30 HCAPLUS COPYRIGHT 2001 ACS
AN 1996:606806 HCAPLUS
DN 125:265951
TI Inhibition of collagen type I synthesis by skin **fibroblasts** of graft versus host disease and scleroderma patients: Effect of **halofuginone**
AU Halevy, Orna; **Nagler, Arnon**; Levi-Schaffer, Francesca; Genina, Olga; **Pines, Mark**
CS Department Animal Science, Faculty Agriculture, Hebrew Univ. Jerusalem, Rehovot, Israel
SO Biochem. Pharmacol. (**1996**), 52(7), 1057-1063
CODEN: BCPCA6; ISSN: 0006-2952
DT Journal
LA English
CC **1-12** (Pharmacology)
Section cross-reference(s): 3
AB The effect of **halofuginone** (a plant alkaloid) on collagen .alpha.1(I) gene expression and collagen synthesis was evaluated in human skin **fibroblasts** from patients with chronic graft-vs.-host disease (cGvHD) or scleroderma and from a normal individual. **Halofuginone** caused a dose-dependent inhibition in collagen .alpha.1(I) gene expression and collagen synthesis in all cultures tested,

the cGvHD **fibroblasts** being the least sensitive. In normal and scleroderma **fibroblasts**, concns. of **halofuginone** as low as 10-10 M and 10-9 M were sufficient to cause a significant redn. in collagen .alpha.1(I) gene expression and collagen synthesis, resp. In addn., **halofuginone** also inhibited transforming growth factor .beta.-induced collagen synthesis. Three days after **halofuginone** removal, collagen gene expression returned to control levels. The redn. of collagen mRNA transcript levels by **halofuginone** appeared to be dependent on new protein synthesis because simultaneous treatment of **fibroblasts** with protein synthesis inhibitors prevents the suppressive effect of **halofuginone** on collagen .alpha.1(I) mRNA gene expression. The ability of extremely low concns. of **halofuginone** to inhibit collagen .alpha.1(I) synthesis specifically and transiently at the transcriptional level suggests that this material may be an important tool for studying collagen .alpha.1(I) gene regulation and may be used as a novel and promising **antifibrotic** therapy.

ST human collagen type I synthesis **halofuginone**; gene expression mRNA translation collagen **halofuginone**

IT **Gene**, animal
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(collagen type I .alpha.1 chain, expression of; inhibition by **halofuginone** of collagen type I synthesis in skin **fibroblasts** of graft vs. host disease and scleroderma patients)

IT Ribonucleic acids, messenger
RL: BOC (Biological occurrence); BPR (Biological process); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(encoding collagen type I .alpha.1 chain, transcription of; inhibition by **halofuginone** of collagen type I synthesis in skin **fibroblasts** of graft vs. host disease and scleroderma patients)

IT **Fibroblast**
(inhibition by **halofuginone** of collagen type I synthesis in skin **fibroblasts** of graft vs. host disease and scleroderma patients)

IT **Fibrosis**
(potential therapeutic role of **halofuginone** in; inhibition by **halofuginone** of collagen type I synthesis in skin **fibroblasts** of graft vs. host disease and scleroderma patients)

IT Translation, **genetic**
(role of in **halofuginone** action upon collagen mRNA expression; inhibition by **halofuginone** of collagen type I synthesis in skin **fibroblasts** of graft vs. host disease and scleroderma patients)

IT **Connective tissue**
(disease, scleroderma, inhibition by **halofuginone** of collagen type I synthesis in skin **fibroblasts** of graft vs. host disease and scleroderma patients)

IT Transplant and Transplantation
(graft-vs.-host reaction, inhibition by **halofuginone** of collagen type I synthesis in skin **fibroblasts** of graft vs. host disease and scleroderma patients)

IT **Collagens, biological studies**
RL: BOC (Biological occurrence); BPR (Biological process); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(type I, .alpha.1 chain; inhibition by **halofuginone** of collagen type I synthesis in skin **fibroblasts** of graft vs. host disease and scleroderma patients)

IT **55837-20-2, Halofuginone**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(inhibition by **halofuginone** of collagen type I synthesis in skin **fibroblasts** of graft vs. host disease and scleroderma patients)

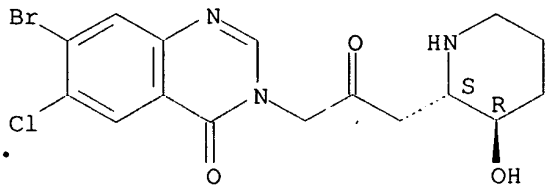
IT **55837-20-2, Halofuginone**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)

(inhibition by **halofuginone** of collagen type I synthesis in skin **fibroblasts** of graft vs. host disease and scleroderma patients)

RN 55837-20-2 HCAPLUS

CN 4(3H)-Quinazolinone, 7-bromo-6-chloro-3-[3-[(2R,3S)-3-hydroxy-2-piperidinyl]-2-oxopropyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L145 ANSWER 26 OF 30 HCAPLUS COPYRIGHT 2001 ACS

AN 1996:483653 HCAPLUS

DN 125:132773

TI Quinazolinone-containing pharmaceutical compositions and methods for the use thereof

IN **Nagler, Arnon**; Slavin, Shimon; **Vlodavsky, Israel**; **Pines, Mark**

PA Davidson, M. Clifford, USA; Agricultural Res. Organization, Ministry of Agriculture; Hadasit Med. Res. Serv. and Development Co. Ltd.

SO PCT Int. Appl., 30 pp.
CODEN: PIXXD2

DT Patent

LA English

IC ICM A61K031-505

CC **1-8** (Pharmacology)

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9619224	A1	19960627	WO 1995-US16932	19951221 <--
	W: AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	IL 112125	A1	19980208	IL 1994-112125	19941222 <--
	CA 2207097	AA	19960627	CA 1995-2207097	19951221 <--
	AU 9646465	A1	19960710	AU 1996-46465	19951221 <--
	AU 693652	B2	19980702		
	EP 794780	A1	19970917	EP 1995-944408	19951221 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	CN 1176601	A	19980318	CN 1995-196904	19951221 <--
	JP 10511939	T2	19981117	JP 1995-520035	19951221 <--
	US 5998422	A	19991207	US 1997-860946	19970623 <--
PRAI	IL 1994-112125		19941222 <--		
	WO 1995-US16932		19951221 <--		

OS MARPAT 125:132773

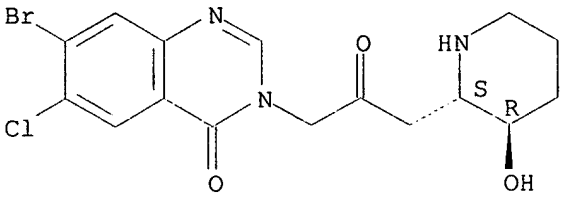
AB The invention provides a compn. contg. quinazolinones, preferably **halofuginone** (I), effective to attenuate mesangial cell proliferation. Sparsely seeded glomerular mesangial cells were exposed to a 10 % FCS in the presence of I; 60-70 % inhibition of mesangial cell proliferation was obtained at 25 ng/mL with an almost complete inhibition at 50 ng/mL.

ST mesangial cell proliferation inhibitor **halofuginone**

IT Kidney, disease
(focal segmental glomerulosclerosis, quinazolinones for attenuation of

mesangial cell proliferation)
IT Kidney
(mesangium, quinazolinones for attenuation of mesangial cell proliferation)
IT **55837-20-2, Halofuginone**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(quinazolinones for attenuation of mesangial cell proliferation)
IT **55837-20-2, Halofuginone**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(quinazolinones for attenuation of mesangial cell proliferation)
RN 55837-20-2 HCAPLUS
CN 4(3H)-Quinazolinone, 7-bromo-6-chloro-3-[3-[(2R,3S)-3-hydroxy-2-piperidinyl]-2-oxopropyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

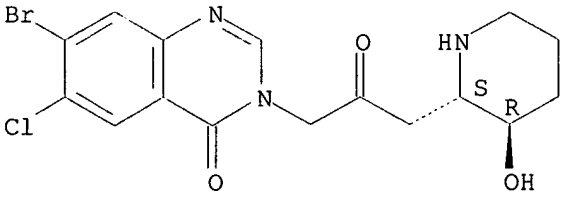


L145 ANSWER 27 OF 30 HCAPLUS COPYRIGHT 2001 ACS
AN 1996:328603 HCAPLUS
DN 125:1389
TI Quinazolinone pharmaceuticals for prevention of restenosis
IN **Nagler, Arnon**; Slavin, Shimon; **Vlodavsky, Israel**; **Pines, Mark**
PA Davidson, Clifford M., USA; Ministry of Agriculture, State of Israel; Hadasit Med. Res. Services and Development Co.
SO PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-505
CC **1-8** (Pharmacology)
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9606616	A1	19960307	WO 1995-US11186	19950829 <--
	W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM				
	RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	IL 110831	A1	19981227	IL 1994-110831	19940831 <--
	CA 2198875	AA	19960307	CA 1995-2198875	19950829 <--
	AU 9536268	A1	19960322	AU 1995-36268	19950829 <--
	AU 692307	B2	19980604		
	EP 787000	A1	19970806	EP 1995-933731	19950829 <--
	EP 787000	B1	20001108		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	CN 1163566	A	19971029	CN 1995-195353	19950829 <--
	JP 10513149	T2	19981215	JP 1995-508990	19950829 <--
	AT 197401	E	20001111	AT 1995-933731	19950829 <--
	US 5891879	A	19990406	US 1996-722046	19961209 <--
PRAI	IL 1994-110831	A	19940831 <--		
	WO 1995-US11186	W	19950829 <--		

OS MARPAT 125:1389
AB The invention provides a pharmaceutical compn. for preventing restenosis by the inhibition of vascular smooth muscle cell (SMC) proliferation, comprising 2-piperidinyl-2-oxopropyl-4(3H)-quinazolinone derivs., preferably **halofuginone** (I). SMCs isolated from the bovine aortic media were seeded in well culture plates in DMEM in the presence of increasing concns. of I; 80-90% inhibition of SMC proliferation was obtained in the presence of 75 ng I/mL, with an almost complete inhibition at 125 ng/mL.
ST piperidinyloxopropylquinazolinone restenosis inhibition; **halofuginone** vascular smooth muscle proliferation inhibition
IT **Artery**
(vascular smooth muscle proliferation inhibition; piperidinyloxopropylquinazolinone for prevention of restenosis)
IT Heart, disease
(restenosis, piperidinyloxopropylquinazolinone for prevention of restenosis)
IT **55837-20-2, Halofuginone**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(piperidinyloxopropylquinazolinone for prevention of restenosis)
IT **55837-20-2, Halofuginone**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(piperidinyloxopropylquinazolinone for prevention of restenosis)
RN 55837-20-2 HCAPLUS
CN 4(3H)-Quinazolinone, 7-bromo-6-chloro-3-[3-[(2R,3S)-3-hydroxy-2-piperidinyl]-2-oxopropyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L145 ANSWER 28 OF 30 HCAPLUS COPYRIGHT 2001 ACS
AN 1996:163378 HCAPLUS
DN 124:250172
TI Inhibition of collagen synthesis and changes in skin morphology in murine graft-versus-host disease and tight skin mice: Effect of **halofuginone**
AU Levi-Schaffer, Francesca; **Nagler, Arnon**; Slavin, Shimon; Knopov, Viktor; **Pines, Mark**
CS Department Pharmacology, Hebrew University Jerusalem, Israel
SO J. Invest. Dermatol. (**1996**), 106(1), 84-8
CODEN: JIDEAE; ISSN: 0022-202X
DT Journal
LA English
CC **1-7** (Pharmacology)
AB The effect of **halofuginone**, a plant alkaloid known to inhibit collagen type I synthesis, on skin collagen content and skin morphol. was evaluated in two in vivo models of scleroderma: the murine chronic graft-vs.-host disease (cGvHD) and the tight skin mouse. Skin collagen was assessed by hydroxyproline levels in skin biopsies and by immunohistochem. using anti-collagen type I antibodies. Daily i.p. injections of **halofuginone** (1 .mu.g/mouse) for 52 d starting 3 d before spleen cell transplantation, abrogated the increase in skin collagen and prevented the thickening of the dermis and the loss of the subdermal fat, all of which are characteristic of the cGvHD mice. **Halofuginone** had a minimal effect on collagen content of the

control mice. The **halofuginone**-dependent decrease in skin collagen content was concn.-dependent and was not accompanied by changes in body wt. in either the cGvHD or the control mice. Injections of **halofuginone** (1 .mu.g/mouse) for 45 d caused a decrease in the collagen content and dermis width in tight skin mice, but did not affect the dermis width of control mice. Collagen content detn. from skin biopsies confirmed the immunohistochem. results in the same mice. The low concn. of **halofuginone** needed to prevent collagen deposition in **fibrotic** skin without affecting body wt. suggests that **halofuginone** may serve as a novel and promising anti-**fibrotic** therapy.

ST **halofuginone** collagen synthesis skin morphol scleroderma

IT **Skin**
(**halofuginone** effects on collagen synthesis and skin morphol. in murine graft-vs.-host disease and tight skin mice)

IT **Connective tissue**
(disease, scleroderma, **halofuginone** effects on collagen synthesis and skin morphol. in murine graft-vs.-host disease and tight skin mice)

IT Transplant and Transplantation
(graft-vs.-host reaction, **halofuginone** effects on collagen synthesis and skin morphol. in murine graft-vs.-host disease and tight skin mice)

IT **Collagens, biological studies**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(type I, **halofuginone** effects on collagen synthesis and skin morphol. in murine graft-vs.-host disease and tight skin mice)

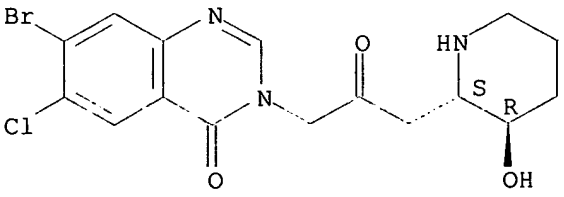
IT **55837-20-2, Halofuginone**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**halofuginone** effects on collagen synthesis and skin morphol. in murine graft-vs.-host disease and tight skin mice)

IT **55837-20-2, Halofuginone**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**halofuginone** effects on collagen synthesis and skin morphol. in murine graft-vs.-host disease and tight skin mice)

RN 55837-20-2 HCAPLUS

CN 4(3H)-Quinazolinone, 7-bromo-6-chloro-3-[3-[(2R,3S)-3-hydroxy-2-piperidinyl]-2-oxopropyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L145 ANSWER 29 OF 30 HCAPLUS COPYRIGHT 2001 ACS

AN 1995:854329 HCAPLUS

DN 123:246878

TI **Antifibrotic** quinazolinone-containing compositions

IN **Pines, Mark**; **Nagler, Arnon**; Slavin, Shimon

PA Ministry of Agriculture, Israel; Hadasit Medical Research Service and Development Co.Ltd.

SO U.S., 23 pp.
CODEN: USXXAM

DT Patent

LA English

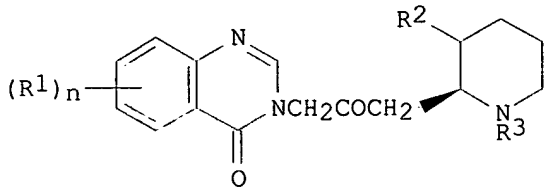
IC ICM A61K031-505

NCL 514259000

CC **1-12** (Pharmacology)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5449678	A	19950912	US 1994-181066	19940114 <--

OS MARPAT 123:246878
GI



I

AB **Antifibrotic** 4-quinazolinones I (R1 = H, halo, NO2, benzo, lower alkyl, Ph, lower alkoxy; R2 = OH, OAc, lower alkoxy; R3 = H, lower alkenoxycarbonyl; n = 1, 2) inhibit collagen type I synthesis and are useful in treatment of scleroderma, pulmonary and hepatic **fibrosis**, and graft-vs.-host disease. Thus, in BALB/c mice with chronic graft-vs.-host disease induced by i.v. injection of spleen cells from B10.D2 mice, the skin collagen content was diminished by i.p. injection of **halofuginone** [I; (R1)n = 6-Cl, 7-Br; R2 = trans-OH; R3 = H] (1 .mu.g/day for 45 days).

ST quinazolinone **fibrosis** treatment; **halofuginone** **fibrosis** treatment

IT **Fibrosis**
(**antifibrotic** quinazolinone-contg. compns.)

IT **Connective tissue**
(disease, scleroderma, **antifibrotic** quinazolinone-contg. compns.)

IT Transplant and Transplantation
(graft-vs.-host reaction, **antifibrotic** quinazolinone-contg. compns.)

IT **Collagens, biological studies**
RL: BPR (Biological process); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(type I, .alpha.2 chain; **antifibrotic** quinazolinone-contg. compns.)

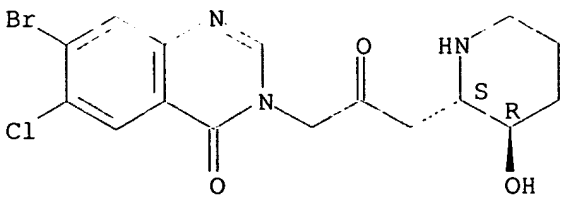
IT **55837-20-2, Halofuginone**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**antifibrotic** quinazolinone-contg. compns.)

IT **55837-20-2, Halofuginone**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**antifibrotic** quinazolinone-contg. compns.)

RN 55837-20-2 HCAPLUS

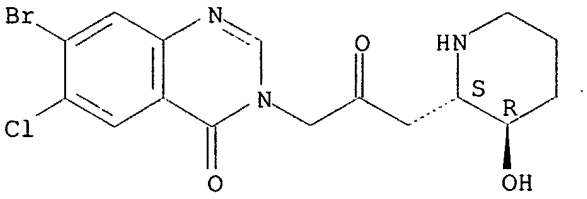
CN 4(3H)-Quinazolinone, 7-bromo-6-chloro-3-[3-[(2R,3S)-3-hydroxy-2-piperidinyl]-2-oxopropyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L145 ANSWER 30 OF 30 HCAPLUS COPYRIGHT 2001 ACS
AN 1993:231169 HCAPLUS
DN 118:231169
TI **Halofuginone**: An inhibitor of collagen type I synthesis
AU Granot, I.; Halevy, O.; Hurwitz, S.; **Pines, M.**
CS Inst. Anim. Sci., Agric. Res. Organ., The Volcani Cent., Bet Dagan, Israel
SO Biochim. Biophys. Acta (**1993**), 1156(2), 107-12
CODEN: BBACAQ; ISSN: 0006-3002
DT Journal
LA English
CC 13-7 (Mammalian Biochemistry)
Section cross-reference(s): **1**, 12
AB The effect of **halofuginone** - a plant alkaloid used as a coccidiostat in birds - on collagen metab. was studied in various avian and mammalian cell cultures. In avian skin **fibroblasts**, **halofuginone** attenuated the incorporation of [3H]proline into collagenase-digestible proteins (CDP) at concns. as low as 10-11 M, without affecting prodn. of [3H]collagenase-non-digestible proteins (NCDP), cell proliferation or collagen degrdn. **Halofuginone** depressed specifically the expression of .alpha.1 gene of collagen type I but not that of collagen type II. This was demonstrated in skin **fibroblasts** and growth-plate chondrocytes using probes contg. inserts sequences corresponding to the .alpha.1(I) and .alpha.1(II) mRNAs. A slight inhibition of the expression of .alpha.2(I) was obsd. in avian skin **fibroblasts** but not in growth-plate chondrocytes. The inhibition of gene expression of both polypeptides of collagen type I in skin **fibroblasts** resulted in a decrease in synthesis, as demonstrated by immunopptn. with specific type I collagen antiserum. In primary cultures of mouse skin **fibroblasts**, avian epiphyseal growth plate chondrocytes and a rat embryo cell line - all of which produce and secrete collagen type I, **halofuginone** inhibited the incorporation of [3H]proline into CDP, the Rat-1 line being the most sensitive to the drug. These results suggest that **halofuginone** affects specifically type I collagen synthesis by repressing gene expression. The need for extremely low concns. of **halofuginone** to inhibit collagen type I synthesis, regardless of the **tissue** or animal species, contributes to the potential usefulness of the substance in studying collagen metab.
ST **halofuginone** collagen I formation gene expression
IT **Gene**, animal
RL: BIOL (Biological study)
(for collagen type I .alpha.-chains, expression of, **halofuginone** inhibition of)
IT **Collagens, biological studies**
RL: FORM (Formation, nonpreparative)
(type I, formation of, **halofuginone** inhibition of, .alpha.-chain gene expression in)
IT **55837-20-2**
RL: BIOL (Biological study)
(collagen type I formation inhibition by, gene expression in)
IT **55837-20-2**
RL: BIOL (Biological study)
(collagen type I formation inhibition by, gene expression in)
RN 55837-20-2 HCAPLUS
CN 4(3H)-Quinazolinone, 7-bromo-6-chloro-3-[3-[(2R,3S)-3-hydroxy-2-piperidinyl]-2-oxopropyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



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FROM JANUARY 1969 TO DATE.

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for details.

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L151 ANSWER 1 OF 8 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2000:499876 BIOSIS
DN PREV200000499997
TI **Halofuginone**: A potent inhibitor of critical steps in **angiogenesis** progression.
AU Elkin, M. (1); Miao, H.-Q.; Aingorn, E.; Reich, R.; Nagler, A.; Pines, M.; Vlodavsky, I.
CS (1) Departments of Oncology, Pharmacology, and Bone Marrow Transplantation, Hadassah-Hebrew University Hospital, Jerusalem, 91120 Israel
SO Clinical & Experimental Metastasis, (1999) Vol. 17, No. 9, pp. 775. print.
Meeting Info.: **VIII International Congress of the Metastasis Research Society** London, UK September 24-27, 2000
ISSN: 0262-0898.
DT **Conference**
LA English
SL English
CC Neoplasms and Neoplastic Agents - Pathology; Clinical Aspects; Systemic Effects *24004
Pathology, General and Miscellaneous - Therapy *12512
Pharmacology - General *22002
Neoplasms and Neoplastic Agents - Therapeutic Agents; Therapy *24008
General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals *00520
IT Major Concepts
Pharmacology; Tumor Biology
IT Diseases
cancer: drug-induced critical **angiogenesis** step inhibition, neoplastic disease
IT Chemicals & Biochemicals
halofuginone: **angiogenesis** inhibiting agent, antineoplastic - drug
IT Alternate Indexing
Neoplasms (MeSH)
IT Miscellaneous Descriptors
Meeting Abstract; Meeting Poster
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name

mouse (Muridae): animal model
ORGN Organism Superterms
Animals; Chordates; Mammals; Nonhuman Mammals; Nonhuman Vertebrates; Rodents; Vertebrates
RN **55837-20-2 (HALOFUGINONE)**

L151 ANSWER 2 OF 8 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1999:346794 BIOSIS
DN PREV199900346794
TI **Halofuginone** (Halo) a specific inhibitor of **collagen** alpha1(I): From the laboratory to the clinic.
AU Nagler, Arnon (1); Fussman, Anat (1); Pines, Mark (1)
CS (1) Volcani Center and Collgard Biopharmaceutical, Hadassah University Hospital, Hadassah Israel
SO Journal of Autoimmunity, (1999) No. SUPPL., pp. 85.
Meeting Info.: **2nd International Congress on Autoimmunity** Tel Aviv, Israel March 7-11, 1999
ISSN: 0896-8411.
DT **Conference**
LA English
CC Immunology and Immunochemistry - General; Methods *34502
Genetics and Cytogenetics - Human *03508
Biochemical Studies - General *10060
Biophysics - General Biophysical Studies *10502
Integumentary System - General; Methods *18501
Pharmacology - General *22002
Pathology, General and Miscellaneous - Therapy *12512
General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals *00520
BC Hominidae 86215
IT Major Concepts
Clinical Immunology (Human Medicine, Medical Sciences); Pharmacology
IT Diseases
scleroderma: connective tissue disease, integumentary system disease; GVHD [graft-vs-host disease]: immune system disease
IT Chemicals & Biochemicals
collagen-alpha-1: gene expression; **halofuginone** [halo]: **collagen** inhibitor
IT Alternate Indexing
Graft vs Host Disease (MeSH)
IT Miscellaneous Descriptors
Meeting Abstract; Meeting Poster
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae): patient
ORGN Organism Superterms
Animals; Chordates; Humans; Mammals; Primates; Vertebrates
RN **55837-20-2 (HALOFUGINONE)**

L151 ANSWER 3 OF 8 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1999:270388 BIOSIS
DN PREV199900270388
TI **Halofuginone**: An inhibitor of **collagen** type I synthesis and of **angiogenesis** inhibits brain tumor growth in vivo.
AU Siegal, Tali (1); Nagler, Arnon (1); Pines, Mark; Vlodavsky, Israel
CS (1) Jerusalem Israel
SO Neurology, (**April 12, 1999**) Vol. 52, No. 6 SUPPL. 2, pp. A424.
Meeting Info.: **51st Annual Meeting of the American Academy of Neurology** Toronto, Ontario, Canada April 17-24, 1999 American Academy of Neurology
. ISSN: 0028-3878.
DT **Conference**
LA English
CC Pharmacology - General *22002

Pathology, General and Miscellaneous - Therapy *12512
Nervous System - General; Methods *20501
Neoplasms and Neoplastic Agents - General *24002
General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals *00520
Biochemical Studies - General *10060
BC Muridae 86375
IT Major Concepts
Nervous System (Neural Coordination); Pharmacology; Tumor Biology
IT Diseases
brain tumor: neoplastic disease, treatment, nervous system disease
IT Chemicals & Biochemicals
collagen type I: synthesis inhibition; **halofuginone**
: antineoplastic - drug
IT Alternate Indexing
Brain Neoplasms (MeSH)
IT Miscellaneous Descriptors
angiogenesis: inhibition; tumor growth: inhibition;
Meeting Abstract; Meeting Poster
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
Fischer rat (Muridae): animal model
ORGN Organism Superterms
Animals; Chordates; Mammals; Nonhuman Mammals; Nonhuman Vertebrates; Rodents; Vertebrates
RN **55837-20-2 (HALOFUGINONE)**

L151 ANSWER 4 OF 8 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1997:184592 BIOSIS
DN PREV199799483795
TI Inhibition of anastomotic intimal hyperplasia by a specific **collagen** type I inhibitor.
AU Callow, A. (1); Choi, E.; Shgal, N.; Brown, D.; Mathieu, J.; Ryan, U.
CS (1) Boston Univ., Boston, MA 02118 USA
SO FASEB Journal, (1997) Vol. 11, No. 3, pp. A155.
Meeting Info.: **Annual Meeting of the Professional Research Scientists on Experimental Biology 97** New Orleans, Louisiana, USA April 6-9, 1997
ISSN: 0892-6638.
DT **Conference; Abstract**
LA English
CC Cytology and Cytochemistry - Animal *02506
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Metabolism - Proteins, Peptides and Amino Acids *13012
Cardiovascular System - General; Methods *14501
Cardiovascular System - Physiology and Biochemistry *14504
Cardiovascular System - Blood Vessel Pathology *14508
BC Leporidae *86040
IT Major Concepts
Cardiovascular System (Transport and Circulation); Cell Biology; Metabolism
IT Chemicals & Biochemicals
HALOFUGINONE HYDROBROMIDE
IT Miscellaneous Descriptors
CARDIOVASCULAR SYSTEM; CAROTID ARTERY; CIRCULATORY SYSTEM; **HALOFUGINONE** HYDROBROMIDE; INHIBITION OF ANASTOMOTIC INTIMAL HYPERPLASIA; SMOOTH MUSCLE CELL PROLIFERATION; SPECIFIC **COLLAGEN** TYPE I INHIBITOR
ORGN Super Taxa
Leporidae: Lagomorpha, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
rabbit (Leporidae)
ORGN Organism Superterms
animals; chordates; lagomorphs; mammals; nonhuman mammals; nonhuman vertebrates; vertebrates

RN **64924-67-0 (HALOFUGINONE** HYDROBROMIDE)

L151 ANSWER 5 OF 8 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1997:55946 BIOSIS
DN PREV199799355149
TI Inhibition of **collagen** synthesis, smooth muscle cell proliferation and injury induced intimal hyperplasia by **halofuginone.**
AU Nagler, A.; Hau-Quan, M.; Pines, M.; Vlodavsky, L.
CS BMT Oncology, Hadassah Univ. Hosp., Jerusalem Israel
SO Blood, (1996) Vol. 88, No. 10 SUPPL. 1 PART 1-2, pp. 57B.
Meeting Info.: **Thirty-eighth Annual Meeting of the American Society of Hematology** Orlando, Florida, USA December 6-10, 1996
ISSN: 0006-4971.
DT **Conference; Abstract**
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Cytology and Cytochemistry - Animal *02506
Biochemical Studies - General 10060
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Cardiovascular System - Blood Vessel Pathology *14508
Pharmacology - Cardiovascular System *22010
BC Bovidae 85715
Leporidae 86040
Muridae *86375
IT Major Concepts
Cardiovascular System (Transport and Circulation); Cell Biology; Pharmacology
IT Chemicals & Biochemicals
HALOFUGINONE
IT Miscellaneous Descriptors
ANIMAL MODEL; CARDIOVASCULAR SYSTEM; CARDIOVASCULAR-DRUG; **COLLAGEN** SYNTHESIS; **HALOFUGINONE**; INHIBITION; INJURY; INJURY INDUCED INTIMAL HYPERPLASIA; PHARMACOLOGY; SMOOTH MUSCLE CELL PROLIFERATION; VASCULAR DISEASE
ORGN Super Taxa
Bovidae: Artiodactyla, Mammalia, Vertebrata, Chordata, Animalia; Leporidae: Lagomorpha, Mammalia, Vertebrata, Chordata, Animalia; Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
bovine (Bovidae); rabbit (Leporidae); rat (Muridae)
ORGN Organism Superterms
animals; artiodactyls; chordates; lagomorphs; mammals; nonhuman mammals; nonhuman vertebrates; rodents; vertebrates
RN **55837-20-2 (HALOFUGINONE)**

L151 ANSWER 6 OF 8 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1997:55412 BIOSIS
DN PREV199799354615
TI Local administration of **halofuginone**, a specific inhibitor of **collagen** type alpha-1 (I) synthesis, ameliorates skin manifestations in a patient with extensive severe chronic graft versus host disease (cGVHD.
AU Nagler, A. (1); Levi-Schaffer, F.; Halvey, O.; Pines, M.
CS (1) BMT, Hadassah, Jerusalem Israel
SO Blood, (1996) Vol. 88, No. 10 SUPPL. 1 PART 1-2, pp. 608A.
Meeting Info.: **Thirty-eighth Annual Meeting of the American Society of Hematology** Orlando, Florida, USA December 6-10, 1996
ISSN: 0006-4971.
DT **Conference; Abstract; Conference**
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Cytology and Cytochemistry - Human *02508
Genetics and Cytogenetics - Human *03508

Pathology, General and Miscellaneous - Therapy *12512
Metabolism - Proteins, Peptides and Amino Acids *13012
Integumentary System - Pathology *18506
Pharmacology - Integumentary System, Dental and Oral Biology *22020
Immunology and Immunochemistry - Immunopathology, Tissue Immunology *34508
Pharmacognosy and Pharmaceutical Botany *54000
BC Hominidae *86215
IT Major Concepts
Cell Biology; Clinical Immunology (Human Medicine, Medical Sciences); Dermatology (Human Medicine, Medical Sciences); Genetics; Metabolism; Pathology; Pharmacognosy (Pharmacology); Pharmacology
IT Chemicals & Biochemicals
HALOFUGINONE
IT Miscellaneous Descriptors
ADULT; ANTIFIBROTIC; **COLLAGEN** TYPE ALPHA-1; DERMATOLOGY; GENE EXPRESSION; GRAFT-VERSUS-HOST DISEASE; **HALOFUGINONE**; IMMUNE SYSTEM DISEASE; LOCAL OINTMENT ADMINISTRATION; PATIENT; PHARMACOLOGY; PLANT ALKALOID; SKIN FIBROBLAST; SKIN MANIFESTATION; SYNTHESIS
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae)
ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates
RN **55837-20-2 (HALOFUGINONE)**

L151 ANSWER 7 OF 8 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1997:54643 BIOSIS
DN PREV199799353846
TI Reduction of pulmonary fibrosis by **halofuginone**, a specific inhibitor of **collagen** type I.
AU Nagler, A. (1); Firman, N.; Pines, M.; Shoshan, S.
CS (1) BMT Connective Tissue Res. Lab., Hadassah, Jerusalem Israel
SO Blood, (1996) Vol. 88, No. 10 SUPPL. 1 PART 1-2, pp. 416A.
Meeting Info.: **Thirty-eighth Annual Meeting of the American Society of Hematology** Orlando, Florida, USA December 6-10, 1996
ISSN: 0006-4971.
DT **Conference; Abstract; Conference**
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Biochemical Studies - General 10060
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Pathology, General and Miscellaneous - Therapy *12512
Respiratory System - Pathology *16006
Pharmacology - Clinical Pharmacology *22005
Pharmacology - Respiratory System *22030
BC Hominidae *86215
IT Major Concepts
Pathology; Pharmacology; Pulmonary Medicine (Human Medicine, Medical Sciences)
IT Chemicals & Biochemicals
HALOFUGINONE
IT Miscellaneous Descriptors
COLLAGEN TYPE I; **HALOFUGINONE**; PATIENT; PHARMACOLOGY; PULMONARY FIBROSIS; PULMONARY MEDICINE; REDUCTION; RESPIRATORY SYSTEM DISEASE; SPECIFIC **COLLAGEN** INHIBITOR; TREATMENT
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae)
ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates
RN **55837-20-2 (HALOFUGINONE)**

L151 ANSWER 8 OF 8 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1995:424122 BIOSIS
DN PREV199598438422
TI **Halofuginone**, a specific inhibitor of **collagen** type I synthesis, is a potential new therapy for chronic graft versus host disease (cGVHD.
AU Nagler, A. (1); Levi-Schaffer, F.; Halevy, O.; Pines, M.
CS (1) Dep. Bone Marrow Transplantation and Anim. Sci., Hadassah Univ. Hosp. Israel
SO Experimental Hematology (Charlottesville), (1995) Vol. 23, No. 8, pp. 806. Meeting Info.: **24th Annual Meeting of the International Society for Experimental Hematology** Duesseldorf, Germany August 27-31, 1995 ISSN: 0301-472X.
DT **Conference**
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Cytology and Cytochemistry - Human *02508
Genetics and Cytogenetics - Human *03508
Biochemical Studies - General 10060
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines 10062
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Replication, Transcription, Translation *10300
Pathology, General and Miscellaneous - Therapy 12512
Metabolism - Proteins, Peptides and Amino Acids *13012
Bones, Joints, Fasciae, Connective and Adipose Tissue - Pathology *18006
Pharmacology - Drug Metabolism; Metabolic Stimulators *22003
Pharmacology - Immunological Processes and Allergy *22018
Pharmacology - Integumentary System, Dental and Oral Biology *22020
Immunology and Immunochemistry - Immunopathology, Tissue Immunology *34508
Plant Physiology, Biochemistry and Biophysics - Chemical Constituents *51522
Pharmacognosy and Pharmaceutical Botany *54000
BC Hominidae 86215
Muridae *86375
IT Major Concepts
Biochemistry and Molecular Biophysics; Cell Biology; Clinical Immunology (Human Medicine, Medical Sciences); Genetics; Metabolism; Molecular Genetics (Biochemistry and Molecular Biophysics); Pharmacognosy (Pharmacology); Pharmacology; Skeletal System (Movement and Support)
IT Chemicals & Biochemicals
HALOFUGINONE
IT Miscellaneous Descriptors
COLLAGEN-ALPHA I GENE EXPRESSION; DERMATOLOGICAL-DRUG; **HALOFUGINONE**; HUMAN SKIN FIBROBLAST; IMMUNOLOGIC-DRUG; **MEETING ABSTRACT**; **MEETING POSTER**; METABOLIC-DRUG; NATURAL PRODUCT; SKIN FIBROSIS
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia; Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
mouse (Muridae); Hominidae (Hominidae)
ORGN Organism Superterms
animals; chordates; humans; mammals; nonhuman mammals; nonhuman vertebrates; primates; rodents; vertebrates
RN **55837-20-2 (HALOFUGINONE)**

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L185 ANSWER 1 OF 18 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 2000003440 EMBASE
TI Topical treatment of cutaneous chronic graft versus host disease with **halofuginone**: A novel inhibitor of **collagen** type I synthesis.
AU Nagler A.; Pines M.
CS A. Nagler, Dept. of Bone Marrow Transplantation, Hadassah University Hospital, Jerusalem, Israel
SO Transplantation, (15 Dec 1999) 68/11 (1806-1809).
Refs: 9
ISSN: 0041-1337 CODEN: TRPLAU
CY United States
DT Journal; Article
FS 009 Surgery
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LA English
SL English
AB Background. In chronic graft-versus-host disease (cGvHD), skin fibrosis, contractures, and an increase in **collagen** content form the hallmark. We report a successful treatment of a cGvHD patient by topical application of **halofuginone**, an inhibitor of **collagen** .alpha.1(I) gene expression. Methods. **Halofuginone**-containing ointment was applied daily on the left side of the neck and shoulder of a cGvHD patient. **Collagen** .alpha.1(I) gene expression and **collagen** content in skin biopsy specimens were evaluated by in situ hybridization and sirius red staining, respectively. Results. After 3 and 6 months, a marked reduction in skin **collagen** synthesis was observed, accompanied with increase neck rotation on the treated side. After cessation of treatment, the sclerosis, skin tightness, and **collagen** .alpha.1(I) gene expression returned to baseline level. No adverse effects were observed, and no plasma levels of **halofuginone** could be detected. Conclusions. **Halofuginone** may provide a promising novel and safe therapy for cGvHD patients.
CT Medical Descriptors:
*graft versus host reaction: CO, complication
*graft versus host reaction: DT, drug therapy
*skin transplantation
skin fibrosis: CO, complication
collagen synthesis
drug safety
human
male
case report
adult
article
priority journal
Drug Descriptors:
***halofuginone: AD, drug administration**
***halofuginone: DT, drug therapy**
***halofuginone: PD, pharmacology**
RN **(halofuginone) 55837-20-2, 64924-67-0, 7695-84-3**

L185 ANSWER 2 OF 18 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 1999297382 EMBASE
TI Inhibition of matrix metalloproteinase-2 expression and bladder carcinoma

metastasis by **halofuginone**.

AU Elkin M.; Reich R.; Nagler A.; Aingorn E.; Pines M.; De-Groot N.; Hochberg A.; Vlodavsky I.
CS I. Vlodavsky, Department of Oncology, Hadassah Hospital, P. O. Box 12000, Jerusalem 91120, Israel. vlodavsk@cc.huji.ac.il

SO Clinical Cancer Research, (1999) 5/8 (1982-1988).
Refs: 46
ISSN: 1078-0432 CODEN: CCREF4
CY United States
DT Journal; Article
FS 016 Cancer
030 Pharmacology
037 Drug Literature Index
LA English
SL English

AB **Matrix** metalloproteinase-2 (MMP-2) plays a critical role in tumor cell invasion and metastasis. Inhibitors of this enzyme effectively suppress tumor metastasis in experimental animals and are currently being tested in clinical trials. MMP-2 transcriptional regulation is a part of a delicate balance between the expression of various **extracellular matrix** (ECM) constituents and ECM degrading enzymes. **Halofuginone**, a low-molecular-weight quinazolinone alkaloid, is a potent inhibitor of **collagen** type .alpha.1 (I) gene expression and ECM deposition. We now report that expression of the MMP-2 gene by murine (MBT2-t50) and human (5637) bladder carcinoma cells is highly susceptible to inhibition by **halofuginone**. Fifty percent inhibition was obtained in the presence of as little as 50 ng/ml **halofuginone**. This inhibition is due to an effect of **halofuginone** on the activity of the MMP-2 promoter, as indicated by a pronounced suppression of chloramphenicol acetyltransferase activity driven by the MMP-2 promoter in transfected MBT2 cells. There was no effect on chloramphenicol acetyltransferase activity driven by SV40 promoter in these cells. **Halofuginone**-treated cells failed to invade through reconstituted basement-membrane (**Matrigel**) coated filters, in accordance with the inhibition of MMP-2 gene expression. A marked reduction (80-90%) in the lung colonization of MBT2 bladder carcinoma cells was obtained after the i.v. inoculation of **halofuginone**-treated cells as compared with the high metastatic activity exhibited by control untreated cells. Under the same conditions, there was almost no effect of **halofuginone** on the rate of MBT2 cell proliferation. These results indicate that the potent antimetastatic activity of **halofuginone** is due primarily to a transcriptional suppression of the MMP-2 gene, which results in a decreased enzymatic activity, **matrix** degradation, and tumor cell extravasation. This is the first description, to our knowledge, of a drug that inhibits experimental metastasis through the inhibition of MMP-2 at the transcriptional level. Combined with its known inhibitory effect on **collagen** synthesis and ECM deposition, **halofuginone** is expected to exert a profound anticancerous effect by inhibiting both the primary tumor stromal support and metastatic spread.

CT Medical Descriptors:
***bladder carcinoma**
metastasis
protein expression
enzyme inhibition
cell invasion
extracellular matrix
collagen synthesis
antineoplastic activity
cancer invasion
human
nonhuman
controlled study
human cell
animal cell
article

priority journal
Drug Descriptors:
*gelatinase a
***halofuginone: AN, drug analysis**
***halofuginone: PD, pharmacology**
quinazolinone derivative
RN (gelatinase a) 146480-35-5; **(halofuginone) 55837-20-2, 64924-67-0, 7695-84-3**

L185 ANSWER 3 OF 18 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 1999292612 EMBASE
TI Inhibition of bladder carcinoma angiogenesis, stromal support, and tumor growth by **halofuginone**.
AU Elkin M.; Ariel I.; Miao H.-Q.; Nagler A.; Pines M.; De-Groot N.; Hochberg A.; Vlodavsky I.
CS I. Vlodavsky, Department of Oncology, Hadassah Hospital, P.O. Box 12000, Jerusalem 91120, Israel. vlodavsk@cc.huji.ac.il
SO Cancer Research, (15 Aug 1999) 59/16 (4111-4118).
Refs: 46
ISSN: 0008-5472 CODEN: CNREA8
CY United States
DT Journal; Article
FS 016 Cancer
028 Urology and Nephrology
037 Drug Literature Index
LA English
SL English
AB We have previously demonstrated that **halofuginone**, a widely used alkaloid coccidiostat, is a potent inhibitor of **collagen** .alpha.1(I) and **matrix** metalloproteinase 2 gene expression. **Halofuginone** also suppresses **extracellular matrix** deposition and cell proliferation. We investigated the effect of **halofuginone** on transplantable and chemically induced mouse bladder carcinoma. In both systems, oral administration of **halofuginone** resulted in a profound anticancerous effect, even when the treatment was initiated at advanced stages of tumor development. Although **halofuginone** failed to prevent proliferative preneoplastic alterations in the bladder epithelium, it inhibited further progression of the chemically induced tumor into a malignant invasive stage. Histological examination and in situ analysis of the tumor tissue revealed a marked decrease in blood vessel density and in both **collagen** .alpha.1(I) and H19 gene expression. H19 is regarded as an early marker of bladder carcinoma. The antiangiogenic effect of **halofuginone** was also demonstrated by inhibition of microvessel formation in vitro. We attribute the profound antitumoral effect of **halofuginone** to its combined inhibition of the tumor stromal support, vascularization, invasiveness, and cell proliferation.
CT Medical Descriptors:
***angiogenesis**
***bladder carcinoma: DT, drug therapy**
***bladder carcinoma: PC, prevention**
***cancer inhibition**
cell proliferation
in situ hybridization
bladder carcinogenesis: DT, drug therapy
bladder carcinogenesis: PC, prevention
antineoplastic activity
cancer growth
drug effect
drug efficacy
nonhuman
male
mouse
animal experiment
animal model
animal tissue

oral drug administration
article
priority journal
Drug Descriptors:
***halofuginone: DT, drug therapy**
***halofuginone: PD, pharmacology**
RN **(halofuginone) 55837-20-2, 64924-67-0, 7695-84-3**
CO Roussel Uclaf (France)

L185 ANSWER 4 OF 18 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 1999261200 EMBASE
TI Liver fibrogenesis and the role of hepatic stellate cells: New insights and prospects for therapy.
AU Li D.; Friedman S.L.
CS S.L. Friedman, Box 1123, Mount Sinai School of Medicine, 1425 Madison Ave, New York, NY 10029-6574, United States. frieds02@doc.mssm.edu
SO Journal of Gastroenterology and Hepatology, (1999) 14/7 (618-633).
Refs: 220
ISSN: 0815-9319 CODEN: JGHEEO
CY Australia
DT Journal; General Review
FS 006 Internal Medicine
037 Drug Literature Index
048 Gastroenterology
LA English
SL English
AB Hepatic fibrosis is a **wound**-healing response to chronic liver injury, which if persistent leads to cirrhosis and liver failure. Exciting progress has been made in understanding the mechanisms of hepatic fibrosis. Major advances include: (i) characterization of the components of **extracellular matrix** (ECM) in normal and fibrotic liver; (ii) identification of hepatic stellate cells as the primary source of ECM in liver fibrosis; (iii) elucidation of key cytokines, their cellular sources, modes of regulation, and signalling pathways involved in liver fibrogenesis; (iv) characterization of key **matrix** proteases and their inhibitors; (v) identification of apoptotic mediators in stellate cells and exploration of their roles during the resolution of liver injury. These advances have helped delineate a more comprehensive picture of liver fibrosis in which the central event is the activation of stellate cells, a transformation from quiescent vitamin A-rich cells to proliferative, fibrogenic and contractile myofibroblasts. The progress in understanding fibrogenic mechanisms brings the development of effective therapies closer to reality. In the future, targeting of stellate cells and fibrogenic mediators will be a mainstay of antifibrotic therapy. Points of therapeutic intervention may include: (i) removing the injurious stimuli; (ii) suppressing hepatic inflammation; (iii) down-regulating stellate cell activation; and (iv) promoting **matrix** degradation. The future prospects for effective antifibrotic treatment are more promising than ever for the millions of patients with chronic liver disease worldwide.
CT Medical Descriptors:
***liver injury**
***liver fibrosis: CO, complication**
*fibrogenesis
*stellate cell
disease course
liver cirrhosis: CO, complication
liver failure
extracellular matrix
cytokine release
protein expression
liver cell
apoptosis
cell activation
blast transformation

myofibroblast
drug targeting
treatment planning
oxidative stress
review
priority journal
Drug Descriptors:
*cytokine: EC, endogenous compound
*matrix metalloproteinase: EC, endogenous compound
*tissue inhibitor of metalloproteinase: EC, endogenous compound
*antifibrotic agent
*antioxidant
*cytokine antibody
retinoid: EC, endogenous compound
corticosteroid
interleukin 1 receptor blocking agent
tumor necrosis factor alpha receptor
ursodeoxycholic acid
prostaglandin e
colchicine
colchiceine
interleukin 10
gamma interferon
alpha tocopherol
resveratrol
quercetin
acetylcysteine
silymarin
transforming growth factor beta receptor
endothelin receptor antagonist
arginylglycylaspartic acid
relaxin
halofuginone
hydroxymethylglutaryl coenzyme a reductase
pentoxifylline
lufironil
unindexed drug
RN (tissue inhibitor of metalloproteinase) 97837-28-0; (ursodeoxycholic acid) 128-13-2, 2898-95-5; (prostaglandin e) 11042-70-9; (colchicine) 64-86-8; (colchiceine) 1990-46-1, 477-27-0; (gamma interferon) 82115-62-6; (alpha tocopherol) 1406-18-4, 1406-70-8, 52225-20-4, 58-95-7, 59-02-9; (resveratrol) 501-36-0; (quercetin) 117-39-5; (acetylcysteine) 616-91-1; (silymarin) 65666-07-1; (arginylglycylaspartic acid) 99896-85-2; (relaxin) 9002-69-1; (**halofuginone**) **55837-20-2, 64924-67-0, 7695-84-3**; (hydroxymethylglutaryl coenzyme a reductase) 37250-24-1; (pentoxifylline) 6493-05-6; (lufironil) 128075-79-6

L185 ANSWER 5 OF 18 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 1999114788 EMBASE
TI **Halofuginone**, an inhibitor of **collagen** type I synthesis, prevents postoperative **adhesion** formation in the rat uterine horn model.
AU Nagler A.; Genina O.; Lavelin I.; Ohana M.; Pines M.
CS Dr. M. Pines, Institute of Animal Science, ARO, Volcani Center, Bet Dagan 50250, Israel
SO American Journal of Obstetrics and Gynecology, (1999) 180/3 I (558-563). Refs: 25
ISSN: 0002-9378 CODEN: AJOGAH
CY United States
DT Journal; Article
FS 010 Obstetrics and Gynecology
037 Drug Literature Index
LA English
SL English
AB OBJECTIVE: The objective of this study was to evaluate the effects of **halofuginone** - a specific inhibitor of **collagen** type I

synthesis - in preventing uterine horn **adhesion** formation in rats. STUDY DESIGN: **Adhesions** were induced by scraping the rat uterine horns until capillary bleeding occurred. **Halofuginone** was either injected intraperitoneally or administered orally. The number and severity of the **adhesions** were scored. **Collagen** .alpha.(1) gene expression was evaluated by in situ hybridization; total **collagen** was estimated by sirius red staining. **Collagen** synthesis in response to **halofuginone** was evaluated in cells cultured from the **adhesions**. RESULTS: Regardless of the administration procedure, **halofuginone** reduced significantly the number and severity of the **adhesions** in a dose-dependent manner. **Halofuginone** prevented the increase in **collagen** .alpha.1(1) gene expression observed in the rats that underwent this procedure, thus affecting only the newly synthesized **collagen** but not the resident **collagen**, in cells derived from rat uterine horn **adhesions**, **halofuginone** induced dose-dependent inhibition of **collagen** synthesis. CONCLUSIONS: Upregulation of **collagen** synthesis appears to play a critical role in the pathophysiologic mechanism of **adhesion** formation. **Halofuginone** could be used as an important means of understanding the role of **collagen** in **adhesion** formation and might become a novel and promising antifibrotic agent for preventing **adhesion** formation after pelvic surgery.

CT Medical Descriptors:
***adhesion**
*uterus horn
collagen synthesis
scoring system
gene expression
in situ hybridization
cell culture
dose response
extracellular matrix
pregnancy rate
female infertility
nonhuman
female
rat
animal experiment
animal model
controlled study
animal cell
oral drug administration
intraperitoneal drug administration
article
priority journal
Drug Descriptors:
***halofuginone: AD, drug administration**
***halofuginone: DO, drug dose**
***halofuginone: PD, pharmacology**
collagen type 1: EC, endogenous compound

RN **(halofuginone) 55837-20-2, 64924-67-0, 7695-84-3**

CO Roussel Uclaf (France)

L185 ANSWER 6 OF 18 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

AN 1999068013 EMBASE

TI **Collagen** synthesis in atherosclerosis: Too much and not enough.

AU Rekhter M.D.

CS M.D. Rekhter, Dept. of Cardiovascular Therapeutics, Parke-Davis Pharmaceut. Res. Div., Warner-Lambert Company, 2800 Plymouth Road, Ann Arbor, MI 48105, United States. mark.rekhter@wl.com

SO Cardiovascular Research, (1999) 41/2 (376-384).
Refs: 118
ISSN: 0008-6363 CODEN: CVREAU

PUI S 0008-6363(98)00321-6

CY Netherlands
DT Journal; General Review
FS 005 General Pathology and Pathological Anatomy
018 Cardiovascular Diseases and Cardiovascular Surgery
037 Drug Literature Index
LA English
SL English
AB Fibrillar **collagen** is a critical component of atherosclerotic lesions. Uncontrolled **collagen** accumulation leads to arterial stenosis, while excessive **collagen** breakdown combined with inadequate synthesis weakens plaques thereby making them prone to rupture. This review discusses cellular sources of **collagen** synthesis in atherosclerosis, local and systemic factors modulating **collagen** gene expression, as well as temporal and spatial patterns of **collagen** production in human and experimental atherosclerotic lesions.
CT Medical Descriptors:
***collagen synthesis**
*atherosclerosis: DT, drug therapy
*atherosclerosis: ET, etiology
artery occlusion: ET, etiology
collagen degradation
atherosclerotic plaque: ET, etiology
coronary artery thrombosis: CO, complication
coronary artery thrombosis: ET, etiology
gene expression
restenosis: CO, complication
restenosis: ET, etiology
cell type
phenotype
cell proliferation
cell migration
time
macrophage
thrombogenesis
angioplasty
nonhuman
animal model
review
priority journal
Drug Descriptors:
***collagen**
calcium channel blocking agent: DT, drug therapy
nitric oxide donor: DT, drug therapy
dextran: DT, drug therapy
tranilast: DT, drug therapy
protamine: DT, drug therapy
halofuginone: DT, drug therapy
mimosine: DT, drug therapy
RN (**collagen**) 9007-34-5; (dextran) 87915-38-6, 9014-78-2; (tranilast) 53902-12-8; (protamine) 11061-43-1, 9007-31-2, 9012-00-4; (**halofuginone**) **55837-20-2, 64924-67-0, 7695-84-3**; (mimosine) 500-44-7

L185 ANSWER 7 OF 18 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 1998423323 EMBASE
TI **Halofuginone** inhibits neointimal formation of cultured rat aorta in a concentration-dependent fashion in vitro.
AU Liu K.; Sekine S.; Goto Y.; Iijima K.; Yamagishi I.; Kondon K.; Matsukawa M.; Abe T.
CS K. Liu, Department of Cardiovascular Surgery, Akita University School of Medicine, Akita 010-8543, Japan
SO Heart and Vessels, (1998) 13/1 (18-23).
Refs: 24
ISSN: 0910-8327 CODEN: HEVEEO
CY Japan

DT Journal; Article
FS 018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB **Halofuginone**, an anticoccidial quinoazolinone, can specifically inhibit **collagen** type .alpha.1 (I) synthesis and gene expression, and also inhibits cultured smooth muscle cell proliferation. The aim of this study was to investigate the effect of **halofuginone** on neointimal formation of rat aorta after culture in a concentration-dependent manner in vitro. Thoracic aorta of Wistar rats was removed and manipulated to damage the endothelium under sterile conditions, and culture for 15 days in **halofuginone**-free or **halofuginone**-added culture medium (n = 20). Segments of cultured aorta were studied by histologic and immunohistochemical methods. Proliferation of neointimal layers consisting of loose multilayer cellular structure was observed in the **halofuginone**-free control group after 15 days of rat aorta culture, and neointimal formation was significantly decreased as an increasing concentration of **halofuginone** was added. As with precultured fresh aorta, no intimal proliferation was observed in the cultured segments of aorta with 500 ng/ml **halofuginone** added to culture medium. The proliferation of cell nuclear antigen index was significantly higher in the **halofuginone**-free control group than that in the **halofuginone**-added groups. The present results suggest that **halofuginone** can inhibit neointimal formation of rat aorta after culture in a concentration-dependent fashion in vitro.
CT Medical Descriptors:
aorta intima
dose response
tissue culture
thoracic aorta
histology
immunohistochemistry
nonhuman
male
rat
animal tissue
article
priority journal
Drug Descriptors:
***halofuginone**
coccidiostatic agent
RN (**halofuginone**) **55837-20-2, 64924-67-0, 7695-84-3**
CO Hoechst marion roussel (Japan)

L185 ANSWER 8 OF 18 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 1998263783 EMBASE
TI **Halofuginone**-an inhibitor of **collagen** type I synthesis-prevents postoperative formation of abdominal **adhesions**
AU Nagler A.; Rivkind A.I.; Raphael J.; Levi-Schaffer F.; Genina O.; Lavelin I.; Pines M.
CS Dr. M. Pines, Institute of Animal Science, ARO, Volcani Center, Bet Dagan 50250, Israel
SO Annals of Surgery, (1998) 227/4 (575-582).
Refs: 31
ISSN: 0003-4932 CODEN: ANSUA5
CY United States
DT Journal; Article
FS 009 Surgery
037 Drug Literature Index
048 Gastroenterology
LA English

SL English
AB Objective: To evaluate the effects of **halofuginone**, a specific inhibitor of **collagen** type I synthesis, on the postoperative formation of abdominal **adhesions** in rats. Summary Background Data: Postoperative **adhesions** remain the leading cause of small bowel obstruction in the Western world. Surgical trauma causes the release of a serosanguineous exudate that forms a fibrinous bridge between two organs. This becomes ingrown with fibroblasts, and subsequent **collagen** deposition leads to the formation of a permanent **adhesion**. Most of the drugs used have been clinically ineffective, and none has been specific to a particular **extracellular matrix** molecule. Therefore, there are serious concerns about the toxic consequences of interfering with the biosynthesis of other **collagens**, other **matrix** proteins, or vital **collagen**-like molecules. Methods: **Adhesions** were induced by scraping the cecum until capillary bleeding occurred. The **adhesions** were scored 21 days later. **Halofuginone** was either injected intraperitoneally (1 .mu.g/25 g body weight) every day, starting on the day of operation, or added orally at concentrations of 5 or 10 mg/kg, starting 4 days before the operation. **Collagen** .alpha.1 (I) gene expression was evaluated by in situ hybridization, total **collagen** was estimated by Sirius red staining, and **collagen** type III was detected by immunohistochemistry. Results: The **adhesions** formed between the intestinal walls were composed of **collagen** and were populated with cells expressing the **collagen** .alpha.1 (I) gene. Regardless of the administration procedure, **halofuginone** significantly reduced the number and severity of the **adhesions**. **Halofuginone** prevented the increase in **collagen** .alpha.1 (I) gene expression observed in the operated rats, thus reducing **collagen** content to the control level. In fibroblasts derived from abdominal **adhesions**, **halofuginone** induced dose-dependent inhibition of **collagen** .alpha.1 (I) gene expression and **collagen** synthesis. **Collagen** type III levels were not altered by **adhesion** induction or by **halofuginone** treatment. Conclusions: Upregulation of **collagen** synthesis appears to have a critical role in the pathophysiology of postoperative **adhesions**. **Halofuginone**, an inhibitor of **collagen** type I synthesis, could be used as an important tool in understanding the role of **collagen** in **adhesion** formation, and it may become a novel and promising antifibrotic agent for preventing postoperative **adhesion** formation.
CT Medical Descriptors:
***peritoneum adhesion: CO, complication**
***peritoneum adhesion: DT, drug therapy**
***peritoneum adhesion: PC, prevention**
postoperative complication
abdominal surgery
drug effect
collagen synthesis
drug efficacy
nonhuman
male
rat
animal experiment
article
priority journal
Drug Descriptors:
***halofuginone: DT, drug therapy**
***halofuginone: PD, pharmacology**
***collagen type 1: EC, endogenous compound**
RN **(halofuginone) 55837-20-2, 64924-67-0, 7695-84-3**

L185 ANSWER 9 OF 18 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN **1998083185** EMBASE

TI [Fibrogenesis: Pathophysiology and therapeutic approaches].
FIBROGENESE: PATHOPHYSIOLOGIE UND THERAPEUTISCHE ANSATZE.
AU Knittel T.; Saile B.; Ramadori G.
CS Prof. G. Ramadori, Abteilung Gastroenterologie, Zentrum Innere Medizin, Robert Koch Strasse 40, D-37075 Gottingen, Germany
SO Internist, (1998) 39/3 (238-246).
Refs: 50
ISSN: 0020-9554 CODEN: INTEAG
CY Germany
DT Journal; General Review
FS 005 General Pathology and Pathological Anatomy
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
048 Gastroenterology
LA German
SL German
CT Medical Descriptors:
***liver fibrosis: ET, etiology**
*fibrogenesis
pathophysiology
stellate cell
kupffer cell
cytology
extracellular matrix
liver metabolism
cell activation
cell proliferation
phenotype
enzyme activity
human
review
Drug Descriptors:
*scatter factor
*antibody
*antioxidant: PD, pharmacology
growth factor: EC, endogenous compound
retinol: EC, endogenous compound
retinol: PD, pharmacology
platelet derived growth factor: EC, endogenous compound
matrix metalloproteinase: EC, endogenous compound
tissue inhibitor of metalloproteinase: EC, endogenous compound
transforming growth factor alpha: EC, endogenous compound
gamma interferon: EC, endogenous compound
gamma interferon: PD, pharmacology
transforming growth factor beta1: EC, endogenous compound
glial fibrillary acidic protein: EC, endogenous compound
lufironil: PD, pharmacology
halofuginone: PD, pharmacology
RN (scatter factor) 67256-21-7, 72980-71-3; (retinol) 68-26-8, 82445-97-4; (tissue inhibitor of metalloproteinase) 97837-28-0; (gamma interferon) 82115-62-6; (lufironil) 128075-79-6; (**halofuginone**) **55837-20-2, 64924-67-0, 7695-84-3**
CN Hoe 077

L185 ANSWER 10 OF 18 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 1998072537 EMBASE
TI **Halofuginone**: A novel antifibrotic therapy.
AU Pines M.; Nagler A.
CS A. Nagler, Dept. of Bone Marrow Transplantation, Hadassah University Hospital, Jerusalem 91120, Israel
SO General Pharmacology, (1998) 30/4 (445-450).
Refs: 57
ISSN: 0306-3623 CODEN: GEPHDP
PUI S 0306-3623(97)00307-8
CY United States

DT Journal; General Review
FS 013 Dermatology and Venereology
015 Chest Diseases, Thoracic Surgery and Tuberculosis
030 Pharmacology
037 Drug Literature Index
048 Gastroenterology
LA English
SL English
AB 1. Fibrosis is characterized by **extracellular matrix** deposition, of which **collagen** type I is the major constituent. The progressive accumulation of connective tissue resulted in destruction of normal tissue architecture and function. 2. Fibrosis is a common response to various insults or injuries and can be the outcome of any perturbation in the cellular function of any tissue. 3. **Halofuginone** was found to inhibit **collagen** .alpha.1(I) gene expression and **collagen** synthesis in a variety of cell cultures including human fibroblasts derived from patients with excessive skin **collagen** type I synthesis. 4. **Halofuginone** was found to inhibit **collagen** .alpha.1(I) gene expression and **collagen** synthesis in animal models characterized by excessive deposition of **collagen**. In these models, fibrosis was induced in various tissues such as skin, liver, lung, etc. **Halofuginone** was injected intraperitoneally, added to the foodstuff or applied locally. 5. **Halofuginone** decreased skin **collagen** in a chronic graft-versus-host disease patient. 6. The ability of extremely low concentrations of **halofuginone** to inhibit **collagen** .alpha.1(I) synthesis specifically and transiently at the transcriptional level suggests that this material fulfills the criteria for a successful and effective anti-fibrotic therapy.
CT Medical Descriptors:
***fibrosis: CO, complication**
***fibrosis: DT, drug therapy**
***fibrosis: ET, etiology**
collagen synthesis
gene expression
graft versus host reaction
skin fibrosis: CO, complication
skin fibrosis: DT, drug therapy
skin fibrosis: ET, etiology
dose response
liver fibrosis: DT, drug therapy
liver fibrosis: ET, etiology
lung fibrosis: DT, drug therapy
lung fibrosis: ET, etiology
postoperative complication
peritoneum adhesion: CO, complication
peritoneum adhesion: DT, drug therapy
peritoneum adhesion: ET, etiology
tendon surgery
restenosis: CO, complication
restenosis: DT, drug therapy
restenosis: ET, etiology
human
nonhuman
review
priority journal
Drug Descriptors:
***halofuginone: DO, drug dose**
***halofuginone: DT, drug therapy**
***halofuginone: PD, pharmacology**
***collagen type 1: EC, endogenous compound**
RN **(halofuginone) 55837-20-2, 64924-67-0, 7695-84-3**

L185 ANSWER 11 OF 18 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 1998021781 EMBASE

TI Inhibition of glomerular mesangial cell proliferation and **extracellular matrix** deposition by **halofuginone**

AU Nagler A.; Katz A.; Aingorn H.; Miao H.-Q.; Condiotti R.; Genina O.; Pines M.; Vlodavsky I.

CS Dr. I. Vlodavsky, Department of Oncology, Hadassah Hospital, P.O. Box 12000, Jerusalem 91120, Israel

SO Kidney International, (1997) 52/6 (1561-1569).
Refs: 45
ISSN: 0085-2538 CODEN: KDYIA5

CY United States

DT Journal; Article

FS 028 Urology and Nephrology
037 Drug Literature Index

LA English

SL English

AB Mesangial cell proliferation, increased deposition of **collagen**, and expansion of the mesangial **extracellular matrix** (ECM) are key features in the development of mesangioproliferative diseases. **Halofuginone**, a low molecular weight anti-coccidial quinoazolinone derivative, inhibits **collagen** type .alpha.1(I) gene expression and synthesis. We investigated the effect of **halofuginone** on both normal and SV40 transformed mesangial cell proliferation, **collagen** synthesis, and ECM deposition. Proliferation of both cell types was almost completely inhibited in the presence of 50 ng/ml **halofuginone**. The cells were arrested in the late G1 phase of the cell cycle and resumed their normal growth rate following removal of the compound from the culture medium. The antiproliferative effect of **halofuginone** was associated with inhibition of tyrosine phosphorylation of cellular proteins. Similar results were obtained whether the mesangial cells were seeded on regular tissue culture plastic or in close contact with a naturally produced ECM resembling their local environment in vivo. **Halofuginone** also inhibited synthesis and deposition of ECM by mesangial cells as indicated by a substantial reduction in 14C-glycine and Na235SO4 incorporation into the ECM, and by the inhibition of **collagen** type I synthesis and gene expression. It is proposed that by inhibiting **collagen** type I synthesis and **matrix** deposition, **halofuginone** exerts a potent antiproliferative effect that may he applied to inhibit mesangial cell proliferation and **matrix** expansion in a variety of chronic progressive glomerular diseases.

CT Medical Descriptors:
*mesangium cell
*cell proliferation
***extracellular matrix**
glomerulus basement membrane
drug effect
collagen synthesis
cell type
cell cycle g1 phase
vascular smooth muscle
gene expression regulation
membranoproliferative glomerulonephritis
nonhuman
rat
animal cell
article
priority journal
Drug Descriptors:
***halofuginone: PD, pharmacology**
***collagen type 1: CR, drug concentration**

RN **(halofuginone) 55837-20-2, 64924-67-0, 7695-84-3**

L185 ANSWER 12 OF 18 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

AN 97263519 EMBASE

DN 1997263519
TI **Halofuginone**, a specific inhibitor of **collagen** type I synthesis, prevents dimethylnitrosamine-induced liver cirrhosis.
AU Pines M.; Knopov V.; Genina O.; Lavelin I.; Nagler A.
CS M. Pines, Institute of Animal Science, ARO, Volcani Center, Bet Dagan 50250, Israel. vlmpines@-volcani.agri.gov.il
SO Journal of Hepatology, (1997) 27/2 (391-398).
Refs: 44
ISSN: 0168-8278 CODEN: JOHEEC
CY Denmark
DT Journal; Article
FS 037 Drug Literature Index
048 Gastroenterology
LA English
SL English
AB Background/Aims: Hepatic cirrhosis is characterized by excessive deposition of **collagen**, resulting from an increase in type I **collagen** gene transcription. We evaluated the effect of **halofuginone** - a specific inhibitor of **collagen** type .alpha.1(I) gene expression - on dimethylnitrosamine (DMN)- induced fiver fibrosis/cirrhosis in rats. Methods: Fibrosis was induced by intraperitoneal injection of DMN. **Halofuginone** (5 mg/kg) was added to the diet. **Collagen** was stained with Sirius red and **collagen** .alpha.1(I) gene expression was evaluated by in situ hybridization. Results: In control rats, a low level of **collagen** .alpha.1(I) gene expression was observed. A high dose of DMN (1%) caused severe fibrosis, as indicated by induction of **collagen** .alpha.1(I) gene expression and increased liver **collagen** content. Addition of **halofuginone** before the onset of fibrosis, almost completely prevented the increase in **collagen** type I gene expression and resulted in lower liver **collagen** content. Moreover, **halofuginone** partially prevented the marked decrease in liver weight and reduced the mortality rate. At a lower dose of DMN (0.25%), which causes mild fibrosis, **halofuginone** prevented the increase in **collagen** .alpha.1(I) gene expression, prevented the increase in liver **collagen** deposition and reduced plasma alkaline phosphatase activity, all of which are characteristic of liver fibrosis/ cirrhosis. Conclusions: These results suggest that **halofuginone** can be used as an important tool to understand the regulation of the **collagen** .alpha.1(I) gene and may become a novel and promising antifibrotic agent for liver fibrosis/cirrhosis.
CT Medical Descriptors:
***liver cirrhosis**
***liver fibrosis**
animal experiment
animal model
animal tissue
article
collagen synthesis
controlled study
dose response
drug mechanism
gene expression
male
nonhuman
oral drug administration
priority journal
rat
Drug Descriptors:
***collagen type 1**
***halofuginone: AD, drug administration**
***halofuginone: DV, drug development**
***halofuginone: DO, drug dose**
***halofuginone: PD, pharmacology**
dimethylnitrosamine: TO, drug toxicity
RN **(halofuginone) 55837-20-2, 64924-67-0,**

7695-84-3; (dimethylnitrosamine) 62-75-9
CN (1) Stenorol
CO (1) Roussel uclaf (France); Sigma (United States)

L185 ANSWER 13 OF 18 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 97039233 EMBASE
DN 1997039233
TI Inhibition of **collagen** synthesis, smooth muscle cell proliferation, and injury-induced intimal hyperplasia by **halofuginone**.
AU Nagler A.; Miao H.-Q.; Aingorn H.; Pines M.; Genina O.; Vlodavsky I.
CS Dr. I. Vlodavsky, Department of Oncology, Hadassah Hospital, PO Box 12 000, Jerusalem 91120, Israel
SO Arteriosclerosis, Thrombosis, and Vascular Biology, (1997) 17/1 (194-202). Refs: 56
ISSN: 1079-5642 CODEN: ATVBFA
CY United States
DT Journal; Article
FS 018 Cardiovascular Diseases and Cardiovascular Surgery
037 Drug Literature Index
LA English
SL English
AB Proliferation of vascular smooth muscle cells (SMCs) and accumulation of **extracellular matrix** (ECM) components within the arterial wall in response to local injury are important etiologic factors in vascular proliferative disorders such as arteriosclerosis and restenosis after angioplasty. Fibrillar and nonfibrillar **collagens** are major constituents of the ECM that modulate cell shape and proliferative responses and thereby contribute to the pathogenesis of intimal hyperplasia. **Halofuginone**, an anticoccidial quinoazolinone derivative, inhibits **collagen** type I gene expression. We investigated the effect of **halofuginone** on (1) proliferation of bovine aortic endothelial cells and SMCs derived from the same specimen and maintained in vitro, (2) ECM deposition and **collagen** type I synthesis and gene expression, and (3) injury-induced intimal hyperplasia in vivo. DNA synthesis and proliferation of vascular SMCs in response to serum or basic fibroblast growth factor were abrogated in the presence of as little as 0.1 .mu.g/mL **halofuginone**; this inhibition was reversible upon removal of the compound. Under the same conditions, **halofuginone** exerted a relatively small antiproliferative effect on the respective vascular endothelial cells. **Halofuginone** also inhibited the synthesis and deposition of ECM components by vascular SMCs as indicated both by a substantial reduction in the amount of sulfated proteoglycans and **collagen** type I synthesis and gene expression. Local administration of **halofuginone** in the rabbit ear model of crush injury- induced arterial intimal hyperplasia resulted in a 50% reduction in intimal thickening as measured by a morphometric analysis of the neointima/media ratio. The differential inhibitory effect of **halofuginone** on vascular SMCs versus endothelial cells, its inhibition of ECM deposition and **collagen** type I synthesis, and its ability to attenuate injury-induced intimal hyperplasia may place **halofuginone** alone or in combination with other antiproliferative compounds as a potential candidate for prevention of arterial stenosis and accelerated atherosclerosis.
CT Medical Descriptors:
*artery intima proliferation: DT, drug therapy
*artery intima proliferation: PC, prevention
***collagen synthesis**
*vascular smooth muscle
animal cell
arteriosclerosis: PC, prevention
arteriosclerosis: ET, etiology
arteriosclerosis: DT, drug therapy
artery injury
artery occlusion: PC, prevention

artery occlusion: DT, drug therapy
artery wall
article
cell proliferation
dna synthesis
endothelium cell
extracellular matrix
gene expression regulation
nonhuman
priority journal
restenosis: ET, etiology
Drug Descriptors:
***collagen**
***collagen type 1**
***halofuginone: AN, drug analysis**
***halofuginone: DV, drug development**
***halofuginone: DT, drug therapy**
***halofuginone: PD, pharmacology**
RN (**collagen**) 9007-34-5; (**halofuginone**)
55837-20-2, 64924-67-0, 7695-84-3

L185 ANSWER 14 OF 18 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 96319168 EMBASE
DN 1996319168
TI Reduction in pulmonary fibrosis in vivo by **halofuginone**.
AU Nagler A.; Firman N.; Feferman R.; Cotev S.; Pines M.; Shoshan S.
CS Hadassah University Hospital, Ein Kerem, P.O. Box 12000,Jerusalem 91120, Israel
SO American Journal of Respiratory and Critical Care Medicine, (1996) 154/4 I (1082-1086).
ISSN: 1073-449X CODEN: AJCMED
CY United States
DT Journal; Article
FS 015 Chest Diseases, Thoracic Surgery and Tuberculosis
037 Drug Literature Index
LA English
SL English
AB Pulmonary fibrosis is a disorder causing a high mortality rate for which therapeutic options are limited. Therefore, the effect of **halofuginone**, a novel inhibitor of **collagen** type I synthesis, on bleomycin-induced pulmonary fibrosis was studied in rats. Pulmonary fibrosis was induced by intraperitoneal injections of bleomycin for seven consecutive days, and **halofuginone** was administered intraperitoneally every second day during the entire experimental period of 42 d. **Collagen** determination in the lungs and the examination of histologic sections showed that **halofuginone** significantly reduced fibrosis relative to the untreated control rats. We conclude that **halofuginone** is a potent in vivo inhibitor of bleomycin-induced pulmonary fibrosis, and that it may potentially be used as a novel therapeutic agent for the treatment of this dysfunction.
CT Medical Descriptors:
***lung fibrosis: PC, prevention**
***lung fibrosis: ET, etiology**
animal model
animal tissue
article
chronic lung disease: ET, etiology
chronic lung disease: PC, prevention
collagen synthesis
controlled study
drug effect
drug mixture
drug potentiation
intraperitoneal drug administration
male
nonhuman

priority journal
Drug Descriptors:
*bleomycin: AD, drug administration
*bleomycin: CB, drug combination
*bleomycin: CM, drug comparison
***halofuginone: AD, drug administration**
***halofuginone: CB, drug combination**
***halofuginone: CM, drug comparison**
***halofuginone: DV, drug development**
***halofuginone: PD, pharmacology**
RN (bleomycin) 11056-06-7; (**halofuginone**) **55837-20-2, 64924-67-0, 7695-84-3**
CO Lundbeck (Denmark); Hoechst (Germany); Roussel (Germany)

L185 ANSWER 15 OF 18 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 96310789 EMBASE
DN 1996310789
TI Inhibition of **collagen** type I synthesis by skin fibroblasts of graft versus host disease and scleroderma patients: Effect of **halofuginone**.
AU Halevy O.; Nagler A.; Levi-Schaffer F.; Genina O.; Pines M.
CS Institute of Animal Science, Volcani Center, Agricultural Research Organization,Bet Dagan 50250, Israel
SO Biochemical Pharmacology, (1996) 52/7 (1057-1063).
ISSN: 0006-2952 CODEN: BCPCA6
CY United States
DT Journal; Article
FS 005 General Pathology and Pathological Anatomy
013 Dermatology and Venereology
022 Human Genetics
026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature IndexDrug Literature Index
LA English
SL English
AB The effect of **halofuginone** (a plant alkaloid) on **collagen** .alpha.1(I) gene expression and **collagen** synthesis was evaluated in human skin fibroblasts from patients with chronic graft-versus-host disease (cGvHD) or scleroderma and from a normal individual. **Halofuginone** caused a dose-dependent inhibition in **collagen** .alpha.1(I) gene expression and **collagen** synthesis in all cultures tested, the cGvHD fibroblasts being the least sensitive. In normal and scleroderma fibroblasts, concentrations of **halofuginone** as low as 10-10 M and 10-9 M were sufficient to cause a significant reduction in **collagen** .alpha.1(I) gene expression and **collagen** synthesis, respectively. In addition, **halofuginone** also inhibited the transforming growth factor .beta.-induced **collagen** synthesis. Three days after **halofuginone** removal, **collagen** gene expression returned to control levels. The reduction of **collagen** mRNA transcript levels by **halofuginone** appeared to be dependent on new protein synthesis because simultaneous treatment of fibroblasts with protein synthesis inhibitors prevents the suppressive effect of **halofuginone** on **collagen** .alpha.1(I) mRNA gene expression. The ability of extremely low concentrations of **halofuginone** to inhibit **collagen** .alpha.1(I) synthesis specifically and transiently at the transcriptional level suggests that this material may be an important tool for studying **collagen** .alpha.1(I) gene regulation and may be used as a novel and promising antifibrotic therapy.
CT Medical Descriptors:
***collagen synthesis**
*graft versus host reaction
*scleroderma
*skin fibroblast

adult
article
autoimmunity
cell culture
concentration response
controlled study
drug mechanism
fibrosis: ET, etiology
gene control
gene expression
genetic transcription
human
human cell
priority journal
protein synthesis
etiology
Drug Descriptors:
*alkaloid: PD, pharmacology
***collagen type 1: EC, endogenous compound**
***halofuginone: PD, pharmacology**
cycloheximide: PD, pharmacology
dactinomycin: PD, pharmacology
messenger rna: EC, endogenous compound
protein synthesis inhibitor: PD, pharmacology
transforming growth factor beta: PD, pharmacology
RN (**halofuginone**) **55837-20-2, 64924-67-0, 7695-84-3**; (cycloheximide) 642-81-9, 66-81-9; (dactinomycin) 1402-38-6, 1402-58-0, 50-76-0
CO Roussel uclaf (France); Sigma (United States)

L185 ANSWER 16 OF 18 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN **96226047** EMBASE
DN **1996226047**
TI **Halofuginone** hydrobromide.
AU Pines M.; Voldavsky I.; Nagler A.
CS Institute of Animal Science, Agricultural Research Organization, Volcani Center, P.O. Box 6,Bet Dagan 50250, Israel
SO Drugs of the Future, (1996) 21/6 (596-599).
ISSN: 0377-8282 CODEN: DRFUD4
CY Spain
DT Journal; (Short Survey)
FS 030 Pharmacology
037 Drug Literature Index
LA English
CT Medical Descriptors:
***collagen synthesis**
*gene expression regulation
artery muscle
dose response
drug blood level
fibroblast
lung fibrosis: DT, drug therapy
restenosis: DT, drug therapy
restenosis: PC, prevention
short survey
smooth muscle fiber
Drug Descriptors:
***halofuginone: AN, drug analysis**
***halofuginone: DV, drug development**
***halofuginone: DO, drug dose**
***halofuginone: DT, drug therapy**
***halofuginone: PK, pharmacokinetics**
***halofuginone: PD, pharmacology**
collagen
plant extract: AN, drug analysis
plant extract: DV, drug development

plant extract: DT, drug therapy
plant extract: PK, pharmacokinetics
plant extract: PD, pharmacology
RN (**halofuginone**) **55837-20-2, 64924-67-0, 7695-84-3**; (**collagen**) 9007-34-5
CO Roussel uclaf (France)

L185 ANSWER 17 OF 18 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 96046197 EMBASE
DN 1996046197
TI Inhibition of **collagen** synthesis and changes in skin morphology in murine graft-versus-host disease and tight skin mice: Effect of **halofuginone**.
AU Levi-Schaffer F.; Nagler A.; Slavin S.; Knopov V.; Pines M.
CS Institute of Animal Science, The Volcani Center, ARO,Bet Dagan 50250, Israel
SO Journal of Investigative Dermatology, (1996) 106/1 (84-88). ISSN: 0022-202X CODEN: JIDEAE
CY United States
DT Journal; Article
FS 013 Dermatology and Venereology
021 Developmental Biology and Teratology
037 Drug Literature Index
LA English
SL English
AB The effect of **halofuginone**, a plant alkaloid known to inhibit **collagen** type I synthesis, on skin **collagen** content and skin morphology was evaluated in two in vivo models of scleroderma: the murine chronic graft-versus-host disease (cGvHD) and the tight skin mouse. Skin **collagen** was assessed by hydroxyproline levels in skin biopsies and by immunohistochemistry using anti-**collagen** type I antibodies. Daily intraperitoneal injections of **halofuginone** (1 .mu.g/mouse) for 52 d starting 3 d before spleen cell transplantation, abrogated the increase in skin **collagen** and prevented the thickening of the dermis and the loss of the subdermal fat, all of which are characteristic of the cGvHD mice. **Halofuginone** had a minimal effect on **collagen** content of the control mice. The **halofuginone**-dependent decrease in skin **collagen** content was concentration-dependent and was not accompanied by changes in body weight in either the cGvHD or the control mice. Injections of **halofuginone** (1 .mu.g/mouse) for 45 d caused a decrease in the **collagen** content and dermis width in tight skin mice, but did not affect the dermis width of control mice. **Collagen** content determination from skin biopsies confirmed the immunohistochemical results in the same mice. The low concentration of **halofuginone** needed to prevent **collagen** deposition in fibrotic skin without affecting body weight suggests that **halofuginone** may serve as a novel and promising anti-fibrotic therapy.
CT Medical Descriptors:
***fibrosis: PC, prevention**
***fibrosis: DT, drug therapy**
*graft versus host reaction: PC, prevention
*graft versus host reaction: DT, drug therapy
*scleroderma: ET, etiology
*spleen cell
animal experiment
animal model
animal tissue
article
controlled study
intraperitoneal drug administration
mouse
nonhuman
priority journal
Drug Descriptors:
***halofuginone: PD, pharmacology**

***halofuginone: DT, drug therapy**
***halofuginone: DO, drug dose**
collagen
RN (halofuginone) **55837-20-2, 64924-67-0, 7695-84-3**; (**collagen**) 9007-34-5
CO Roussel (France)

L185 ANSWER 18 OF 18 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 95083784 EMBASE
DN 1995083784
TI **Halofuginone**, a specific **collagen** type I inhibitor, reduces anastomotic intimal hyperplasia.
AU Choi E.T.; Callow A.D.; Sehgal N.L.; Brown D.M.; Ryan U.S.; Walsh D.B.; Donahoe P.K.; Sumpio B.E.; Ruby S.T.
CS Division of Vascular Surgery, Department of Surgery, Boston University School of Medicine, 80 E Concord St,Boston, MA 02118, United States
SO Archives of Surgery, (1995) 130/3 (257-261).
ISSN: 0004-0010 CODEN: ARSUAX
CY United States
DT Journal; Article
FS 018 Cardiovascular Diseases and Cardiovascular Surgery
037 Drug Literature Index
LA English
SL English
AB Objective: To determine if **halofuginone** hydrobromide, a specific type I **collagen** inhibitor, could prevent intimal hyperplasia at a vascular anastomosis. Design: Intimal hyperplasia is characterized by smooth muscle cell proliferation and **extracellular matrix** accumulation. **Halofuginone** was used to block **collagen** production and smooth muscle cell proliferation in cell cultures and in a rabbit model of an end-to-end anastomosis of the right common carotid artery. Animals were fed a nontoxic dose of **halofuginone**. Eighteen rabbits were fed the inhibitor in a randomized blinded fashion and were examined after 4 weeks by harvesting the arteries after perfusion fixation at physiologic pressures. Results: **Halofuginone** inhibited smooth muscle cell proliferation in vitro and had no effect on cell viability. Morphometric quantification verified that **halofuginone** treatment significantly attenuated anastomotic intimal thickness. Conclusion: Oral administration of **halofuginone** inhibits intimal hyperplasia at vascular anastomoses. Intimal hyperplasia inhibition by **halofuginone** may be a therapeutic option for preventing arterial stenosis in vascular surgery.
CT Medical Descriptors:
*artery intima proliferation: DT, drug therapy
artery occlusion: DT, drug therapy
article
blood vessel shunt
cell proliferation
cell viability
drug inhibition
extracellular matrix
human
human cell
priority journal
smooth muscle fiber
Drug Descriptors:
***halofuginone: AD, drug administration**
***halofuginone: DO, drug dose**
***halofuginone: DT, drug therapy**
RN (halofuginone) **55837-20-2, 64924-67-0, 7695-84-3**

=> d his

(FILE 'HOME' ENTERED AT 07:46:41 ON 07 NOV 2001)

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                SET COST OFF

     FILE 'REGISTRY' ENTERED AT 07:46:49 ON 07 NOV 2001
L1                  STR
L2               11 S L1
L3              273 S L1 FUL
                    SAV L3 KWON762/A
                    E HALOFUGINONE/CN
L4                1 S E3
L5               27 S L3 AND C16H17BRCLN3O3
                    SEL RN L4
L6               18 S E1/CRN
L7               18 S L5 AND L6
L8                9 S L5 NOT L7
L9                4 S L8 NOT 7 BROMO 6 CHLORO
L10               5 S L8 NOT L9
L11              23 S L4,L6,L7,L10
L12                 STR L1
L13               2 S L12 SAM SUB=L3
L14               2 S L12 CSS SAM SUB=L3
L15              81 S L12 CSS FUL SUB=L3
                    SAV L15 KWON762A/A
L16              58 S L15 NOT L10,L11
L17              57 S L16 NOT C16H16CL3N3O3
L18               1 S L16 NOT L17
L19              80 S L15 NOT L18
L20              80 S L9,L11,L19
L21             193 S L3 NOT L20
L22             179 S L21 AND (NC5 AND NCNC3-C6)/ES
L23              14 S L21 NOT L22

     FILE 'HCAPLUS' ENTERED AT 07:59:36 ON 07 NOV 2001
L24             226 S L20
L25             182 S HALOFUGINON?
L26             238 S L24,L25
                    E PINES M/AU
L27             114 S E3,E4,E5
                    E VLODAVSKY I/AU
L28             216 S E3-E5
                    E VLODAVSK I/AU
L29              10 S E5,E6
                    E NAGLER A/AU
L30             120 S E3,E4,E13,E14
                    E HAZUM E/AU
L31             111 S E3,E4
L32              31 S L26 AND L27-L31
L33               9 S L32 AND EXTRACELLULAR?(L)MATRI?
L34             197 S L26 AND (PD<=19980813 OR PRD<=19980813 OR AD<=19980813)
L35              22 S L32 AND L34
L36               6 S L33 AND L35
L37              22 S L35,L36
L38               9 S L32 NOT L37
L39             209 S L26 AND (PD<=19990813 OR PRD<=19990813 OR AD<=19990813)
L40             205 S L26 AND  PY<=1999
L41             209 S L34,L39,L40
L42              26 S L32 AND L41
L43               5 S L32 NOT L42
                    E COLLAGEN/CW
L44              22 S E3,E4,E7 AND L41
                    E COLLAGEN/CT
                    E E3+ALL
                    E E2+ALL
L45           57946 S E5,E4+NT
L46          211933 S E56+NT
                    E E57+ALL
L47            9447 S E14,E13+NT
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L48       23650 S EXTRACELLULAR?(L)MATRI?
L49           6 S CKROX
                E TRANSCRIPTION FACTOR/CT
                E E63+ALL
L50       74892 S E4,E3+NT
                E E124+ALL
L51       57986 S E4,E3+NT
                E E24+ALL
L52        1373 S E4,E3+NT
                E E10+ALL
L53       57986 S E4,E3+NT
L54         187 S HSP47 OR HSP 47
L55       15100 S HEAT(L)SHOCK(L)PROTEIN
                E HEAT SHOCK PROTEIN/CT
                E HEAT-SHOCK/CT
                E E19+ALL
L56       10421 S E4-E7,E3+NT
                E CYTOKINE/CW
L57       76150 S E3,E4,E6
                E CYTOKINE/CT
                E E6+ALL
L58       17576 S E13,E14,E12+NT
                E E45+ALL
L59      136052 S E5,E4+NT
L60       23881 S IL1B OR (IL OR INTERLEUKIN)(L)(1B OR 1(L)BETA)
L61       35295 S TNFA OR ATNF OR (TNF OR TUMOR(L)NECROSIS(L)FACTOR)(L)ALPHA
L62         123 S  TUMOUR(L)NECROSIS(L)FACTOR(L)ALPHA
L63       10897 S NFKB OR NF(L)(KB OR KAPPA(L)B)
L64        7246 S NUCLEAR FACTOR (L)(KB OR KAPPA(L)B)
L65        1053 S COLLAGENASE(L)TYPE. () (4 OR IV)

    FILE 'REGISTRY' ENTERED AT 08:24:25 ON 07 NOV 2001
L66           1 S 9040-48-6
                E TUMOR NECROSIS FACTOR/CN
L67           1 S E3
                E TUMOR NECROSIS FACTOR-.ALPHA./CN
                E TUMOR NECROSIS FACTOR .ALPHA./CN
L68           1 S E3

    FILE 'HCAPLUS' ENTERED AT 08:25:24 ON 07 NOV 2001
L69         920 S L66,L67,L68
L70          25 S L41 AND L45-L65,L69
L71           5 S GENE/CW AND L41
L72           5 S GENES/CW AND L41
L73           3 S GENETIC/CW AND L41
L74          25 S L70-L73
L75         150 S (1 OR 63 OR 15 OR 26)/SC,SX AND L41
L76          22 S L75 AND L74
L77           3 S L74 NOT L76
L78          29 S L41 AND TISSUE
L79           1 S L41 AND ?TRAUM?
                E ANIMAL TISSUE/CT
                E E3+ALL
L80           9 S L41 AND E3,E2+NT
L81           8 S L80 NOT 17/SC
L82          20 S L78 NOT L80
L83           9 S L82 NOT 17/SC,SX
L84           6 S L83 AND (1 OR 63)/SC,SX NOT CHICKEN
L85           4 S L84 NOT (QUAIL OR RATS)/TI
                E WOUND/CW
L86        9823 S E3,E5
                E WOUND/CT
                E E3+ALL
L87        2469 S E4,E3+NT
                E E8+ALL
L88        5920 S E3,E2+NT
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                E E12+ALL
L89          1809 S E3+NT
                E E7+ALL
                E E10+ALL
L90          5809 S E3,E4,E2+NT
                E E11+ALL
                E E9+ALL
L91           681 S E4+NT
L92        211933 S E3+NT
L93            11 S L41 AND L86-L92
L94             9 S L93 NOT CHICKEN
                E FIBROSIS/CW
L95          6711 S E3
                E FIBROSIS/CT
                E E3+ALL
L96          5481 S E2+NT
L97        169659 S ?FIBRO?
                E LIVER FIBROSIS/CT
                E E3+ALL
                E LIVER FIBROSIS/CT
                E E3+ALL
L98           170 S E1
L99           817 S E2
                E CIRRHOSIS/CW
L100         7041 S E3
                E CIRRHOSIS/CT
                E E3+ALL
L101         6898 S E5,E6,E4+NT
L102        14943 S ?CIRRHO?
L103       140467 S ?INFLAM?
                E INFLAM/CW
L104        58649 S E4,E5
                E INFLAM/CT
                E E8+ALL
L105        59040 S E2+NT
L106        18414 S E57+NT OR E56+NT OR E55
                E E55+ALL
L107        42443 S E4-E7,E2,E11-E16
                E LEUKOTRIENE/CT
                E E27+ALL
L108        10758 S E12,E13,E11+NT
                E E24+ALL
L109          817 S E6,E5+NT
                E KIDNEY FIBROSIS/CT
                E RENAL FIBROSIS/CT
                E E3+ALL
L110          140 S E1
L111          298 S E2
                E PULMONARY FIBROSIS/CT
L112          316 S E3
                E E3+ALL
L113          907 S E2
                E CARDIAC FIBROSIS/CT
                E HEART FIBROSIS/CT
L114         5131 S (HEART OR CARDI? OR MYOCARD?)(L)?FIBRO?
L115          169 S NEOANGIOGEN?
                E ANGIOGEN/CW
L116         6003 S E4
L117          789 S E5
                E ANGIOGEN/CT
                E E4+ALL
L118         4883 S E5+NT
L119         1760 S E7+NT
L120          789 S E8+NT
L121       109153 S E9+NT
L122        13124 S ?ANGIOGEN?
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                E ADHESION/CT
                E E4+ALL
L123        1686 S E1
                E E2+ALL
L124       19574 S E2,E1+NT
L125        7399 S ?PSORIA?
                E PSORIA/CW
L126        5126 S E5
                E PSORIA/CT
                E E6+ALL
L127        5126 S E4+NT
L128         414 S KELOID
                E KELOID/CT
                E E3+ALL
L129         314 S E4+NT
L130        4036 S SCAR OR SCARING
                E SCAR/CW
L131           3 S E3
                E SCAR/CT
                E E5+ALL
L132         216 S E4
L133          29 S L41 AND L95-L132
L134          28 S L133 NOT 17/SC,SX
L135          24 S L134 NOT CHICKEN
                E SKIN/CT
                E E3+ALL
L136          12 S L41 AND E4+NT
L137           0 S L41 AND (E42+NT OR E43+NT)
                E E46+ALL
L138           5 S L41 AND (E4 OR E3+NT)
L139          36 S L42,L76,L79,L81,L85,L94,L135,L136,L138
L140          41 S L43 OR L139
L141          36 S L140 AND (1 OR 63)/SC,SX
L142           5 S L141 AND CHICKEN
L143          31 S L141 NOT L142
L144          30 S L143 NOT 17/SC
L145          30 S L144 AND L24-L65,L69-L143
                SEL HIT RN

     FILE 'REGISTRY' ENTERED AT 08:49:30 ON 07 NOV 2001
L146           2 S E1-E2

     FILE 'REGISTRY' ENTERED AT 08:50:05 ON 07 NOV 2001

     FILE 'HCAPLUS' ENTERED AT 08:50:31 ON 07 NOV 2001

     FILE 'BIOSIS' ENTERED AT 08:51:12 ON 07 NOV 2001
L147         245 S L26
L148         222 S L147 AND PY<=1999
L149          72 S L148 AND (00520/CC OR CONFERENCE/DT OR (CONGRESS OR CONFERENC
L150          17 S L149 NOT (?COCCID? OR CHICKEN OR HEN OR BROILER OR TURKEY OR
L151           8 S L150 AND (COLLAGEN? OR ANGIOGEN?)

     FILE 'BIOSIS' ENTERED AT 08:55:28 ON 07 NOV 2001

     FILE 'EMBASE' ENTERED AT 08:55:49 ON 07 NOV 2001
L152         164 S L26
L153         128 S L152 AND PY<=1999
L154          10 S L153 AND EXTRACELL?(L)MATRI?
                E FIBROSIS/CT
                E E3+ALL
L155       30441 S E3+NT
L156           2 S L153 AND C6.610./CT
L157           8 S L153 AND L155
                E LIVER FIBROSIS/CT
                E E3+ALL
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L158          4 S L153 AND E1+NT
                E CIRRHOSIS/CT
                E E3+ALL
                E E2+ALL
L159          2 S L153 AND E6+NT
                E INFLAMMATION/
                E INFLAMMATION/CT
                E E3+ALL
L160          5 S L153 AND E3+NT
                E KIDNEY FIBROSIS/CT
                E E3+ALL
L161          0 S L153 AND E1+NT
                E PULMONARY FIBROSIS/CT
                E E3+ALL
L162          3 S E2+NT AND L153
                E CARDIAC FIBROSIS/CT
                E E3+ALL
L163          0 S L153 AND E2+NT
                E NEOANGIOGENESIS/CT
                E ANGIOGENESIS/CT
                E E3+ALL
L164          1 S L153 AND E1+NT
                E NEOANGIOGEN? AND L153
L165          0 S NEOANGIOGEN? AND L153
                E ADHESION/CT
                E E3+ALL
L166          1 S E3 AND L153
                E BIOADHESION/CT
L167          3 S ADHESION AND L153
                E PSORIASIS/CT
L168          0 S E3+NT AND L153
                E KELOID/CT
L169          0 S E3+NT AND L153
                E SCAR/CT
                E E3+ALL
L170          0 S E8+NT AND L153
                E WOUND/CT
                E E3+ALL
L171          3 S L153 AND E3+NT
L172          1 S L153 AND WOUND?
L173         20 S L154,L156-L172
                E COLLAGENASE/CT
                E E3+ALL
L174          1 S L153 AND COLLAGENASE
L175         18 S L153 AND COLLAGEN
L176          0 S L153 AND TRANSCRIPTION(L)FACTOR
L177          1 S L153 AND L54,L55,L60-L64,L66-L68
L178          0 S L153 AND L49
L179         25 S L173,L174,L175,L177
L180         23 S L179 NOT (CHICK OR CHICKEN OR BROILER OR HEN OR POULTRY OR FO
L181          7 S L180 NOT AB/FA
                SEL DN 1 2
                SEL AN 1 2
L182          2 S L181 AND E1-E3
L183         16 S L180 NOT L181
L184          2 S L153 AND SKIN FIBROSIS+NT/CT
L185         18 S L182,L183,L184

     FILE 'EMBASE' ENTERED AT 09:08:44 ON 07 NOV 2001
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